"CLINICAL SPECTRUM OF NEONATAL ENCEPHALOPATHY AND THE ROLE OF CPK MB ASSAY IN TRANSIENT MYOCARDIAL ISCHEMIA OF HYPOXIC ISCHEMIC ENCEPHALOPATHY"

Dissertation submitted in partial fulfilment of the

Requirement for the award of the Degree of

DOCTOR OF MEDICINE - BRANCH VII

PAEDIATRIC MEDICINE

APRIL 2015

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI ,

TAMIL NADU.

CERTIFICATE

This is to certify that the Dissertation entitled **"CLINICAL SPECTRUM OF NEONATAL ENCEPHALOPATHY AND THE ROLE OF CPK MB ASSAY IN TRANSIENT MYOCARDIAL ISCHEMIA OF HYPOXIC ISCHEMIC ENCEPHALOPATHY"** submitted by **Dr. M.K.Senthil Kumar, M.B.B.S** to The Tamilnadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the award of M.D.Degree(Paediatrics) is a bonafide work carried out by him under my guidance and supervision during the academic year 2012-2014. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other

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I**, Dr. M.K.Senthil Kumar, M.B.B.S**, solemnly declare that the Dissertation titled **"CLINICAL SPECTRUM OF NEONATAL ENCEPHALOPATHY AND THE ROLE OF CPK MB ASSAY IN TRANSIENT MYOCARDIAL ISCHEMIA OF HYPOXIC ISCHEMIC ENCEPHALOPATHY"** has been prepared by me.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment of the regulations for the award of MD Degree Branch VII (PAEDIATRICS).

It was not submitted to the award of any degree/diploma to any University either in part or in full previously.

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PROTOCOL TITLE: Clinical spectrum of neonatal encephalopathy and the role of CPKMB assay in transient myocardial ischemia of hypoxic ischemic encephalopathy

NAME OF PRINCIPAL INVESTIGATOR: Dr. M.K.Senthil Kumar

DESIGNATION OF PRINCIPAL INVESTIGATOR: Resident in Paediatrics

DEPARTMENT & INSTITUTION: Department of Paediatrics, Tirunelveli Medical College

Dear Dr. M.K.Senthil Kumar, *The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 28.12.13.*

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☑
2.	Study Protocol	☑
3.	Department Research Committee Approval	☑
4.	Patient Information Document and Consent Form in English and Vernacular Language	☑
5.	Investigator's Brochure	☑
6.	Proposed Methods for Patient Accrual Proposed	☑
7.	Curriculum Vitae of the Principal Investigator	☑
8.	Insurance /Compensation Policy	☑
9.	Investigator's Agreement with Sponsor	☑
10.	Investigator's Undertaking	☑
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)	☐
14.	Clinical Trials Registry-India (CTRI) Registration	☑

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 2weeks before for renewal / extension of the validity
4. An annual status report should be submitted
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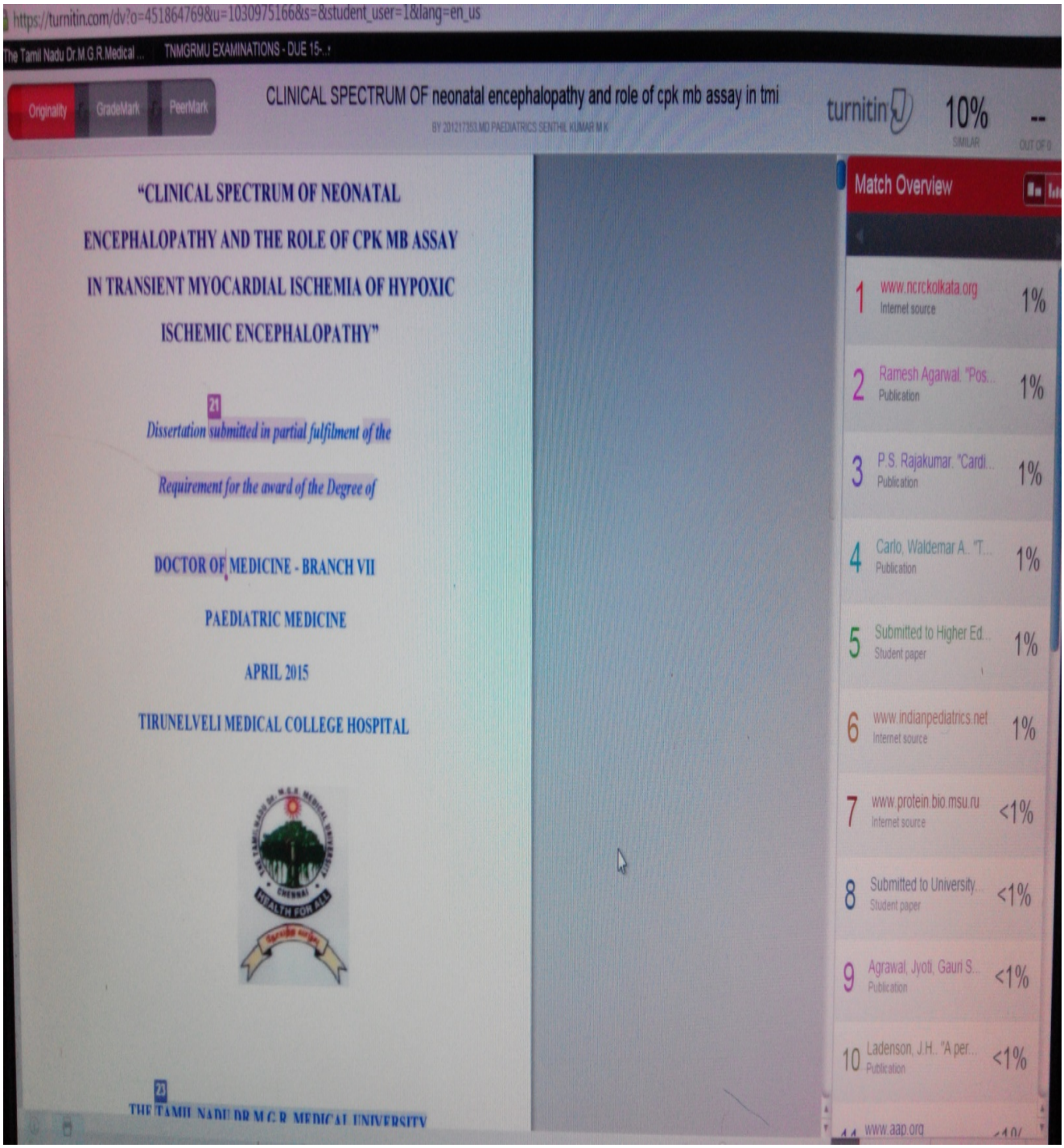
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CONTENTS

CLINICAL SPECTRUM OF NEONATAL ENCEPHALOPATHY AND THE ROLE OF CPK MB ASSAY IN TRANSIENT MYOCARDIAL ISCHEMIA OF HYPOXIC ISCHEMIC ENCEPHALOPATHY

AIM :

To study the various causes of encephalopathy and their outcome in newborns admitted in TVMCH and to evaluate the myocardial dysfunction in neonates having birth asphyxia (HIE) by electrocardiographic study (ECG) and creatine phosphor kinase muscle brain fraction (CPK-MB) assay.

METHODOLOGY:

All term neonates with features of encephalopathy admitted in sick neonatal ward of Government Tirunelveli medical college Hospital for a period of 8 months between January 2014 to august 2014 were included. Babies admitted in the hospital with evidence of asphyxia indicated by any three of the following:

(i) APGAR $\leq$3 at 5 minutes.

(ii) fetal heart rate < 60/min

(iii) Meconium stained amniotic fluid

(iv) need for positive pressure ventilation for >1 min

Exclusion criteria:

(i)Preterm babies,

(ii) Neonates with congenital malformation,

(iii) Neonates mothers who would have received magnesium sulphate injection within 4 hours prior to delivery or received opioids (pharmacological depression) or any other form of sedation.

STUDY PROTOCOL:

After written consent from parents, all the neonates included in study had the

following done:

Detailed maternal history, details of meconium staining of amniotic fluid, birth

events, APGAR score, Sex and weight of the baby recorded. Gestational age of baby assessed by New Ballard scoring system. Detailed clinical and neurological examination were done. Non-invasive blood pressures, perfusion index using pulsoximetry were measured.

Serum creatine phospho kinase MB assay were done at birth, 24 hours and at 72 hours. Chest X-ray was taken to assess cardiomegaly, electrocardiography and where possible echocardiography based on transportability of newborn were done. Treatment as per existing institutional protocol was given.

RESULTS:

During the study period 70 babies had neonatal encephalopathy. Out of which 65 babies had Hypoxic encephalopathy. Others include 2 babies with hypoglycemia, 2 babies with intraventricular haemorrhage and one case of bilirubin encephalopathy.

Further 65 babies with HIE were evaluated for transient myocardial ischemia.Analysis showed the following:

The cases with high CPK MB 24 hours are more likely to have shock than those without high CPK MB 24hours value. The other CPK values are not related to the shock occurrence.

There is no difference in the high CPK-MB value at birth for those with and without cardiomegaly. The case with cardiomegaly is more likely to have high CPK-MB value at 24 hours and 72 hours than in the cases without cardiomegaly.

There is a significant difference in the presence of negative ECHO findings in those with and without high CPK-MB value. The cases with high CPK-MB value are less likely to have a negative ECHO finding.

CONCLUSION:

Neonatal encephalopathy is a common condition in a neonatal intensive care unit. Hypoxic ischemic encephalopathy is the most common cause of neonatal encephalopathy.

Routine ECG monitoring of asphyxiated babies helps to detect myocardial dysfunction and hence the identification of shock.

Assay of cardiac enzyme markers CPK-MB helps to complement clinical evaluation for early identification of shock.

Use of pulsoximeters which measure perfusion index is useful tool for recognition of shock.

KEY WORDS:

Neonatal Encephalopathy, Birth Asphyxia, Transient Myocardial Ischemia, CPK-MB.

1. INTRODUCTION

Neonatal encephalopathy is the term used to represent “an abnormal neurobehavioral state consisting of decreased level of consciousness and usually other signs of brain stem or motor dysfunction”. Hypoxic ischemic encephalopathy or simply birth asphyxia is the major cause of neonatal encephalopathy. In addition to birth asphyxia large numbers of conditions like birth trauma, hypoglycemia, meningitis, bilirubin encephalopathy, inborn errors of metabolism, central nervous system defects accidental local anesthetic intoxication, space occupying lesions, intracranial hemorrhage, etc. produce neonatal encephalopathy. “Failure to initiate or sustain respiration after birth” is the WHO definition for birth asphyxia.

Major advancement have been made in the field of fetal and perinatal medicine by use of newer monitoring technologies but till date birth asphyxia causes prolonged hospitalization due to multiple organ dysfunction and many the times the complications result in death. Even among the survivors brain damage results in developmental delay and spasticity.

In India birth asphyxia causes around 20% of newborn deaths[1].

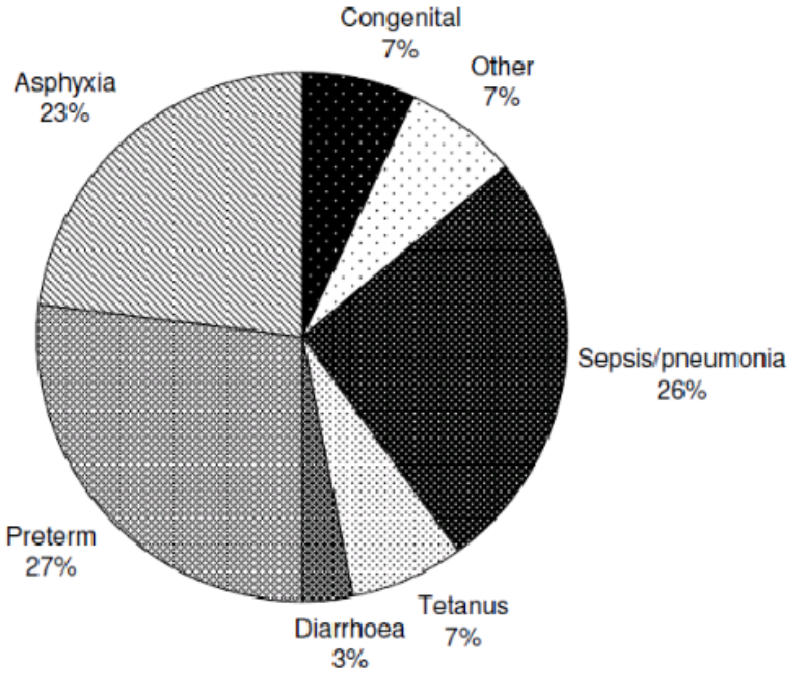


Figure: Estimated distribution of direct causes of 4 million neonatal deaths for the year 2000. [Adapted from Lawn 2005]

LAWN 2005 from LANCET [2]

Perinatal asphyxia affects multiple organs and the features of the affected organ dysfunction slowly manifested clinically. No organ is actually spared. Critical organ dysfunction leads to drastic worsening of the newborn's vital parameters. Early detection of this dysfunction in a neonatal intensive care unit determines the morbidity and mortality.

Late recognition of the critical organ dysfunction results in serious complications and may lead on to death Myocardial ischemia occurring in asphyxiated babies is transient in nature.

2. AIMS AND OBJECTIVES:

AIM :

To study the various causes of encephalopathy and their outcome in newborns admitted in TVMCH and to evaluate the myocardial dysfunction in neonates having birth asphyxia (HIE) by electrocardiographic study and creatine phospho kinase muscle brain fraction (CPK-MB) assay.

OBJECTIVES:

Various causes, presentations of neonatal encephalopathy, methods used for diagnosis and outcome measured with respect to survival. CPK-MB assay along with ECG and clinical evaluation will be analysed to detect the relationship with HIE and outcome.

3. REVIEW OF LITERATURE

The WHO definition of birth asphyxia in the international Classification of diseases (ICD 10) is based on the Apgar scoring system . The ICD -10 definition of birth asphyxia is dependent on the 1minute apgar score .An 1 minute apgar score of 0-3 defines severe birth asphyxia and moderate asphyxia is the baby having an 1 minute Apgar score of 4-7.

The NNPD 2000 defined perinatal asphyxia as “slow gasping breathing or an Apgar score of 4-6 as moderate asphyxia whereas the one with no breathing or an Apgar score of 0-3 at 1 minute as severe asphyxia”.[1]

The National neonatology forum (NNF) of India has used asphyxia as "gasping or ineffective breathing or lack of breathing at one minute of life"[1]

A descriptive term 'birth depression' is used to indicate a newborn with poor Apgars but without passing judgement on etiology. The use of word 'perinatal' rather than 'birth' clarifies that the pathological process that may begin many hours before birth and may continue for many hours afterwards. Causes are numerous and there clinical manifestations vary. Babies who had mild asphyxia may not have any neurological injury.

However a severely asphyxia may be fatal in utero, or immediately after birth, with extensive neurological sequelae with or without cognitive deficits among survivors.

CAUSE FOR DELAY IN RESPIRATION[3]

Factors other than asphyxia that may delay the onset of respiration after delivery.

- Central nervous system injury or abnormality present prior to labour
- Drugs depressing the central nervous system
- Maternal hypocapnia
- Trauma, especially to the central nervous system
- Prematurity, in particular surfactant-deficient, stiff lungs
- Sepsis, especially group B streptococci
- Muscle weakness due to prematurity or primary muscle disease
- Anemia, hypovolemia
- Congenital malformations
    - Obstructing the airway or preventing lung expansion
    - Neurological, impairing respiratory control

The terms that may be used in evaluating a term infant at risk for brain injury in the perinatal period are as follows:

À. Neonatal depression [4]

Its a term used to describe an infant who has a prolonged transition from an intrauterine to an extra uterine environment. 1 min and 5 min Apgar scores are usually low in these infants.

B. Neonatal encephalopathy

Its a clinical term used to describe an abnormal neurobehavioral state that consists of a decreased level of consciousness with abnormalities in neuromotor tone. Characteristic feature is that one that begins within the first postnatal day and may be associated with seizure-like activity, hypoventilation or apnoea, depressed primitive reflexes and the appearance of brain stem reflexes.

It does not imply a specific etiology, nor does it imply a irreversible neurologic injury.

C.Hypoxic-ischemic encephalopathy

HIE is “an abnormal neurobehavioral state in which the predominant pathogenic mechanism is impaired cerebral blood flow”.

D.Hypoxic-ischemic brain injury

It refers to “neuropathology attributable to hypoxia and/or ischemia as evidenced by biochemical (such as serum creatine kinase brain bound [CK BB]), electro physiologic (EEG), neuroimaging (cranial ultrasonography, MRI, CT) or post-mortem abnormalities”.[4]

INCIDENCE:

The occurrence of perinatal asphyxia is in the range of 1% to 1.5% of total live births in western hemisphere, gestational age and birth weight are the two important determinants associated with asphyxia[4]. The higher the birth weight and more the gestational age less likely are asphyxia. The incidence is about 0.5% of live born infants >36 weeks gestation accounting for around 20% of perinatal deaths. It accounts for 50% if stillborns are included. A higher incidence is noted in term IDM infants of diabetic or toxaemic mothers, IUGR babies, post-dated and babies with breech presentations. Of the 26 million births each year in India, 4-6% of neonates fail to establish spontaneous breath at birth[5]. Nearly 8.4% of inborn babies in India have 1 minute Apgar score < 7 and around 1.4% have HIE[6].

ETIOLOGY:

Impaired gas exchange across the placenta is the main problem that leads to insufficient provision of oxygen and removal of carbon dioxide and hydrogen ion (H+) from the foetus results in 90% of asphyxial events during and before the labour period in term infants.

Remainder of these events are secondary to pulmonary, cardiovascular or neurologic abnormalities that occur in postpartum period.

A. Following factors increase the chances of perinatal asphyxia:

1. Decline in mother's oxygenation / Hb saturation
2. Decreased placental blood flow from the mother
3. Decreased blood flow from the placenta to foetus
4. Insufficient gas exchange across the placenta or at the foetal tissue level.
5. Increase in foetal oxygen requirement.

B. Etiologies of perinatal hypoxia-ischemia are

1. Maternal determinants: hypertension (acute or chronic), infection, diabetes, hypotension, vascular disease, drug use and hypoxia due to pulmonary, cardiac or neurologic diseases.
2. Placental causes: infarction, fibrosis, abruption or hydrops.
3. Uterine bleed, rupture.
4. Umbilical cord accidents: cord prolapse, entanglement, true knot , external compression.
5. Abnormalities of umbilical vessels.
6. Foetal factors: low Hb levels, intra uterine infection, cardiac diseases, hydrops, severe cardiac / circulatory insufficiency.
7. Neonatal factors: severe neonatal hypoxia due to cyanotic congenital heart disease, persistent pulmonary hypertension of the newborn (PPHN), cardiomyopathy, other forms of neonatal carcinogenic and/or septic shock.

ADAPTATIONS TO HYPOXIA[7]

Important physiological adaptations to short episodes of fetal hypoxic stress.

Cardiovascular responses:
'Diving seal' reflex
Redistribution of blood flow
Towards brain, myocardium and adrenals
Away from gut, lungs and carcass
Bradycardia
Increase in blood pressure
Regional cerebral blood flow changes:
Relative increase to brainstem
Relative decrease to cerebral cortex
Autonomic responses:
In premature animals-
Net parasympathetic response
In full-term animals-
Net sympathetic response
Cathecholamine surge:
Biochemical response:
Glycolysis
Switch from aerobic to anaerobic metabolism

NEONATAL ENCEPHALOPATHY:

Variety of events acts to predispose the newborn to have encephalopathy. These events may occur during the labour, or even before the onset of labour and may continue in the newborn period or may have onset in the newborn period itself and may cause neonatal encephalopathy. This condition may or may not be associated with seizures. Thus occurrence of seizure is not necessary for making the diagnosis of neonatal encephalopathy.

ACOG 2003 states that “Children certainly may exhibit altered arousal and muscle tones, as well as seizures, without meeting the suggested criteria for HIE from intrapartum causes”. The children can have abnormal neurological findings due to events occurring before birth like factors involving maternal, placental, or foetal diseases (Adamson et al, 1995).

TABLE- SHOWING OTHER CAUSES OF NEONATAL ENCEPHALOPATHY[8]

Infective	Meningitis (bacterial or viral) Encephalitis (herpes simplex)
Traumatic brain lesion	e.g. Subdural hemorrhage
Vascular	Neonatal stroke Shock secondary to acute blood loss (antepartum/intrapartum)
Metabolic	Hypoglycemia Hypo/hypernatremia Bilirubin encephalopathy
Inborn error of metabolism	Urea cycle defects Pyridoxine dependency Lactate acidemias Amino acidemias (non-ketotic hyperglycemia) Organic acidemias
Congenital brain malformation	e.g. Neuronal migration disorder
Neuromuscular disorder	e.g. Spinal muscular atrophy
Maternal drug exposure	Acute or chronic

HYPOGLYCEMIA[9]

Hypoglycaemia according to Cornblath and Schwartz[9], 1967; Milner,1972 is said to be present "if blood glucose levels of less than 20 mg/dL in preterm infants and in less term infants a value less than 30 mg/dL". Sencor, 1973 stated that "No clear consensus exists concerning a direct cause and effect for hypoglycaemia with seizure occurrence".

Methods of glucose determination will affect the accuracy of the value[9] i.e., point of-care blood sampling versus laboratory serum sampling. Because for every one hour of delay in analyzing the sample the blood glucose value falls by 18 mg%. Hence a two hour delay will cause false low value when there is actually no hypoglycaemia in the baby. Sometimes hypoglycaemia may be accompanied low calcium levels, craniocerebral injury, cerebrovascular abnormalities, and birth asphyxia, which results in seizures with much lower threshold. Babies born to mothers with systemic illness like diabetes mellitus/gestational diabetes or pregnancy induced hypertension i.e. IDM, IUGR

Babies also are at risk for hypoglycaemia. This is more evident particularly for those who were not appropriate for gestational age like SGA babies. Hypoglycaemia generally manifests as Jitteriness, apnoea, and altered tone, but that does not mean these babies have seizure.

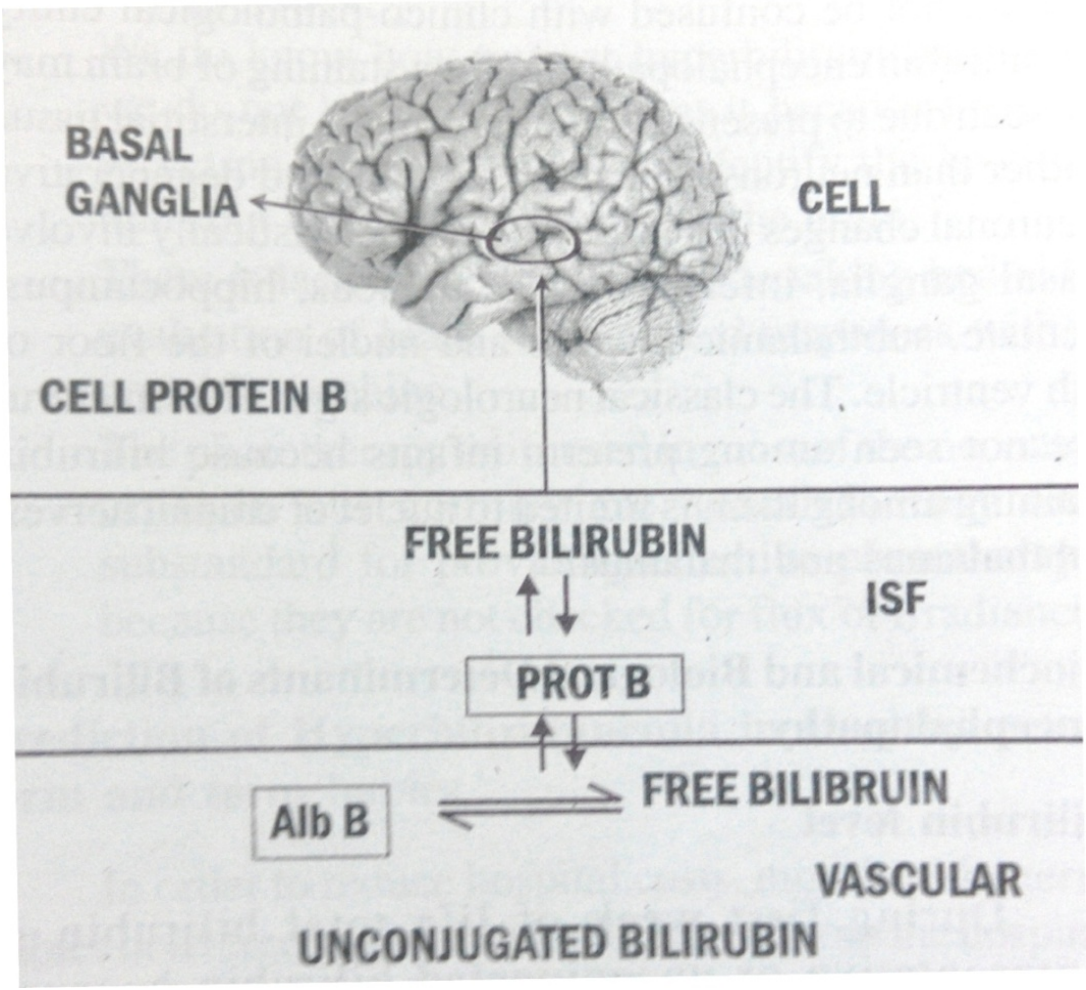
Griffiths and Laurence, 1974 found that “Cerebrovascular lesions in posterior brain regions have been reported in children who suffer hypoglycaemia”.

Siemkowicz and Hansen, in 1978 based on studies in mature animals and Griffiths and Laurence, in 1974 in neonatal infants reported that “Increased vulnerability of brain to ischemic insults is seen when there is concomitant hypoglycaemia”.

HYPERBILIRUBINEMIA

Neonatal jaundice with increased unconjugated bilirubin levels need immediate attention as it has high chances of causing bilirubin encephalopathy or kernicterus. Kernicterus is manifested as poor feeding due to lethargy, initial hypotonia replaced later by hypertonia. Weak or abnormal Moro's response, high temperature, seizures, coma, retrocollis and opisthotonus are the other associated findings. Preterm babies may have sudden apnoea ending fatally without any history of convulsions.

Sugama et al, 2001 stated that "the imaging findings in kernicterus are most apparent on MRI, with hyperintensity at the posterior margin or throughout the globi pallid on T2-weighted sequences". In HIE changes are noted in putamen and thalamus. In kernicterus the area involved is globus pallidus. Recently, Johnston and Hoon, 2000 has suggested that "the high resting neuronal activity in the globus pallidus might make it more vulnerable to less intense, subacute oxidative stresses from mitochondrial toxins such as bilirubin "



BILIRUBIN MOVEMENT IN KERNICTERUS[10]

INTRACRANIAL HAEMORRHAGES:

Intracranial haemorrhages are seen more commonly seen in term asphyxiated and in preterm babies and the incidence of them have declined with the use of antenatal steroids, effective fluid management in asphyxiated babies. Obstructed labour, difficult instrumentation in vaginal delivery (forceps application, vacuum) has been associated uncommonly with traumatic intracranial bleeds[11]. Haemorrhagic disease of newborn is one another condition that can cause intracranial bleed. Clinically these babies present with bulging anterior fontanel, lethargy convulsions, unexplained anaemia and jaundice. Failure of correction of low haematocrit to blood transfusion should alert the paediatrician of intracranial bleeds. Intraventricular haemorrhages are detected using neuroimaging[11]. Progressive hydrocephalus and porencephalic cysts may develop in severe cases.

BIRTH ASPHYXIA:

A gold standard definition of birth asphyxia does not exist. It is probably better to use the term perinatal asphyxia since asphyxia may occur in utero, at birth or in the postnatal period. WHO has defined perinatal asphyxia as a “failure to initiate and sustain breathing at birth” The National Neonatal Perinatal Database (NNPD), 2000 used a similar definition for perinatal asphyxia. It defined moderate asphyxia as slow gasping breathing or an Apgar score of 4-6 at 1 minute of age. Severe asphyxia was defined as no breathing or an Apgar score of 0-3 at 1 minute of age.[1]

Table:4 Clinical Criteria Necessary to Establish That Acute Neurological Injury in the Newborn Was Related to "Asphyxia" Proximate to Delivery [12,13]

Profound metabolic or mixed acidemia (pH<7.0) determined by an umbilical cord arterial sample, if obtained
Apgar score of 0–3 for longer than 5 min
Neonatal neurological manifestations—e.g., seizures, coma, or hypotonia
Multisystem organ dysfunction—e.g., cardiovascular, gastrointestinal, hematological, pulmonary, or renal system

As per the AAP (American academy of Pediatrics) and ACOG (American college of Obstetrics and Gynecology), all the following has to be present to give the term

- Cord blood analysis showing high metabolic or mixed acedemia (pH< 7.00).
- 5 minute Apgar score of 0-3
- Evidence of CNS insults in newborn like convulsions,poor tone, coma.
- Multiple organ involvement e.g, intestinal, cardiac, renal, hepatic, pulmonary dysfunction .

Apgar scores are used to plan treatment in asphyxiated babies by protocols and to explain the prognosis and complications including impairments.

HISTORICAL REVIEW:

Definition of birth asphyxia and its usage varied among the treating physicians, biochemists and pathologists. Dr. Eastman from the famous Hopkins used asphyxia “an infelicity of etymology” because the greek word asphyxia literally meant “without pulse”.

In 1861, Dr. William Little[14] presented his paper stating “ a causal relationship between abnormal parturition and central nervous system damage”[14]. Dr .Little mentioned that we may not appreciate the difference between apoplexy, asthenia and asphyxia, but circulatory failure or the shock was the cause of the central nervous system dysfunction noticed. The words “asphyxia neonaturum” and “suspended animation” were in use at that time. He compared appearance of these asphyxiated newborns with the problems of an adult who had drowning.

MULTIORGAN DYSFUNCTION OF ASPHYXIA:

Perinatal asphyxia affects multiple organs and the features of the affected organ dysfunction slowly manifested clinically . no organ is actually spared.critical organ dysfunction leads to drastic worsening of the newborn's vital parameters. Early detection of these dysfunction in a neonatal intensive care unit determines the morbidity and mortality.

Late recognition of the critical organ dysfunction results in serious complications and may lead on to death.

In asphyxiated newborns kidney is the most commonly affected accounting for nearly 50%. CNS dysfunction seen in 28% of neonates with asphyxia. Heart and pulmonary complications are almost have equal frequency and each noticed in 25% of cases[1] .

Table: 5 Multiorgan Systemic Effects of Asphyxia.[15]

SYSTEM	EFFECT
Central nervous system	Hypoxic-ischemic encephalopathy, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertonia
Cardiovascular	Myocardial ischemia, poor contractility, cardiac stun, tricuspid insufficiency, hypotension
Pulmonary	Pulmonary hypertension, pulmonary hemorrhage, respiratory distress syndrome
Renal	Acute tubular or cortical necrosis
Adrenal	Adrenal hemorrhage
Gastrointestinal	Perforation, ulceration with hemorrhage, necrosis
Metabolic	Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria
Integument	Subcutaneous fat necrosis
Hematology	Disseminated intravascular coagulation

The severity of organ damage decides the prognosis drastically. Low calcium levels, low sodium levels and extremes of blood glucose levels are the commonly encountered metabolic derangements. The low sodium level may be due to direct renal damage or as a consequence of Syndrome of inappropriate anti diuretic hormone. Thrombocytopenia and

disseminated intravascular coagulation are the hematological disturbances commonly seen following asphyxia.

Brain damage following perinatal asphyxia results in a condition described as Hypoxic ischemic encephalopathy (HIE) . This is of great concern to the treating pediatrician as the asphyxiated newborn may suffer from major neuromotor sequelae if the baby survives and discharged from hospital.

Classification of hypoxic ischemic encephalopathy based on its severity is done in a detailed manner by Sarnat and Sarnat[16] and is presented below as tabulation.

Mild (grade I) Encephalopathy:

Hyperalertness , decreased threshold for all stimuli,easily elicted Moro reflex,staring look, seizures will not be there in this stage.

Moderate (grade II) Encephalopathy:

Seizures are common. Lethargy, hypotonia, differential tone in upper and lower limbs. arms are relatively hypotonic than legs.

Severe (grade III) Enceophalopathy:

No spontaneous movementscomatose, frequent and prolonged seizures, sometimes no seizure activity and isoelectric EEG.

Table: 6 Sarnat and Sarnat Stages of Hypoxic-Ischemic Encephalopathy. [16]

Stage	Stage 1 (Mild)	Stage 2 (Moderate)	Stage 3 (Severe)
Level of consciousness	Hyperalert; irritable	Lethargic or obtunded	Stuporous, comatose
Neuromuscular control:	Uninhibited, overreactive	Diminished spontaneous movement	Diminished or absent spontaneous movement
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive, disinhibited	Decreased or absent
Segmental myoclonus	Present or absent	Present	Absent
Complex reflexes:	Normal	Suppressed	Absent
Suck	Weak	Weak or absent	Absent
Moro	Strong, low threshold	Weak, incomplete high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function:	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Midposition, often unequal; poor light reflex
Respirations	Spontaneous	Spontaneous; occasional apnea	Periodic; apnea
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable

Gastrointestinal motility	Normal or decreased	Increased diarrhea	Variable
Seizures	None	Common focal or multifocal (6 to 24 hours of age)	Uncommon (excluding decerebration)
Electroencephalographic findings	Normal (awake)	Early: generalized low-voltage, slowing (continuous delta and theta)	Early: periodic pattern with isopotential phases
		Later: periodic pattern (awake); seizures focal or multifocal; 1.0 to 1.5 Hz spike and wave	Later: totally isopotential
Duration of symptoms	<24 hours	2 to 14 days	Hours to weeks
Outcome	About 100% normal	80% normal; abnormal if symptoms more than 5 to 7 days	About 50% die; remainder with severe sequelae

LEVENE'S CLASSIFICATION[17]:

The grading of HIE by Sarnat and Sarnat is detailed but difficult one. A classification of HIE modified from Sarnat and Sarnat staging of hypoxia is the Levene's classification. This being simplified for easy and immediate assessment of the stage of HIE by just assessing the important factors.This is in common practice in most of neonatal intensive care units.

Table: 7 A clinical grading system for hypoxic-ischaemic encephalopathy by Levene MI.[17]

Feature	Mild	Moderate	Severe
Consciousness	Irritable	Lethargy	Comatose
Tone	Hypotonia	Marked hypotonia	Severe hypotonia
Seizures	No	Yes	Prolonged
Sucking/respiration	Poor suck	Unable to suck	Unable to sustain Spontaneous respiration

CRITERIA FOR ORGAN DYSFUNCTION BY SHAH[18]

Table: 8 . Criteria for organ dysfunction in newborn infants with perinatal asphyxia used by Shah et al 2004.[18]

Renal: anuria or oliguria (< 1ml/kg/h) for 24h or more, and a serum creatinine concentration > 100mmol/L; or anuria/oliguria for > 36h; or any serum creatinine > 125mmol/L; or serial serum creatinine values that increase postnatally
Cardiovascular: hypotension demanding treatment with an inotrope drug for more than 24h to maintain blood pressure within the normal range, or electrocardiographic evidence of transient myocardial ischemia
Pulmonary: need for ventilator support with oxygen requirement > 40% for at least the first four hours after birth
Hepatic: AST > 100U/L or ALT > 100U/L at any time during the first week after birth

TRANSIENT MYOCARDIAL ISCHEMIA:

During asphyxia blood flow to myocardium is preserved but cardiac compromises do occur as a common complication of hypoxic ischemic injury. doppler ultrasound studies are useful in detection of cardiac dysfunction. 28 to 40 % of asphyxiated infants develop cardiac dysfunction[19]. Hypotension with cardiogenic shock, tricuspid incompetency, arrythmia and myocardial ischemia are the recognized complications. The later two are reconised by electrocardiograph. The tricuspid insufficiency is functional and secondary to acute cardiac dilation.ST depression in the mid precordium and T wave inversion in the left precordium. Echocardiographic findings include most commonly decreased left ventricular contractility, high ventricular end-diastolic pressures, tricuspid regurgitation (due to papillary muscle ischemia) and pulmonary hypertension. In severe asphyxia, dysfunction more common affects the right ventricle. A fixed heart rate should alert about the possibility of clinical brain death.

CARDIOVASCUAR RESPONSE IN ASPHYXIA:

Decreased ventricular contractility and decline in cardiac output are the commonly seen changes in prolonged total or partial asphyxia. There is in addition to biochemical and radiological evidence of transient myocardial ischemia ,contractile dysfunction of heart is also noted[20-22]. Myocardium is depleted of adenosine 5'phosphate (ATP) .this ATP depletion is the major event leading to injury during and after ischemia.
In TMI the neonate may present with variety of symptoms. The chid may have tachycardia , tricuspid valve insufficiency murmur, congestive cardiac failure, and in severe cases may have cardiogenic shock[23]. Due to decline in cardiac function the child may develop hypotension following an asphyxia[24].

The neonatal heart has its own glycogen storage from which it glucose is derived by glycogenolysis. Experitemental data suggests that because of this nature the immature heart has capability to recover from short period of ischemia when compared to adult heart[25]. In the myocardium the contraction is initiated by the action of calcium on proteins. In the mature heart the source of calcium is that released from sarcoplasmic reticulum. The condition in newborn rats is different and they are found to be dependent on extra cellular calcium when compared

to adults. The immature heart is thus less sensitive to ischemia compared to the heart of an adult, the reason being the substantial glycogen stores,improved anaerobic metabolism, better exchange of calcium during ischemia and increased amino acid substrate utilization[26]. Histological findings congestion, myocardial and subendocardial hemorrage or necrosis, cardiomyopathy and infarction of the endocardial muscles leading to papillary muscle necrosis are noted in neonates after asphyxia.

HISTOLOGY:

Cardiac muscle is involuntary striated muscle and is specific of myocardium. Cardiomyocytes or otherwise called as myocardiocytes are the cells that form heart musculature. These cells are characterized by the presence of single unique nucleus. Cardiac muscle has cross striations made of thick and thin protein filaments. Actin and myosin are the primary structural proteins of cardiac muscle similar in nature to skeletal muscle.Intercalated discs (IDs) play a major role in connecting electrochemical synctium to hearts myocytes. Release of calcium to the sarcoplasm initiates contraction and reuptake of calcium produces relaxation.

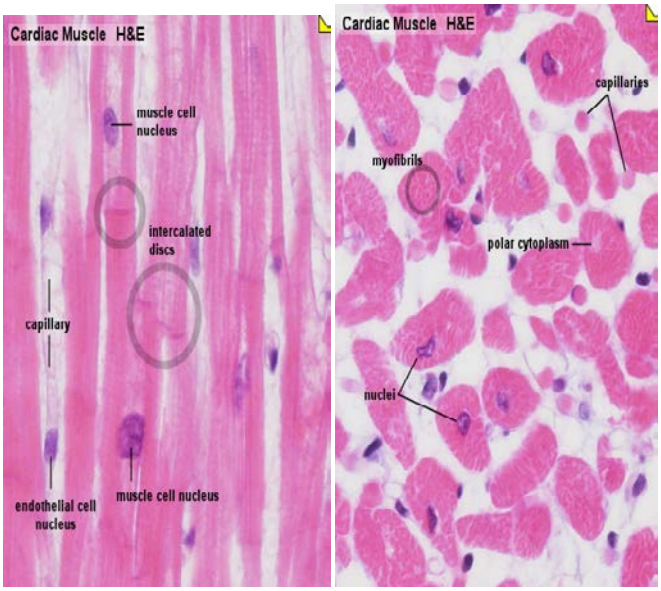


Fig.1 Myocardium (longitudinal section): High power

CARDIAC MUSCLE CONTRACTION

Cardiac muscle contraction occurs by complex termed as regulatory unit. It comprises of Seven actin monomers and tropomyosin dimer in addition to one heterotrimericTroponin complex. Later consisting of Troponin C, Troponin I, and Cardiac TroponinX. .the seven actin monomers are from thin filament. Neighbouring tropomyosins interact among each other because of presence of sticky ends, and a thread, continuous of tropomyosin is seen in the groove of the actin helix.

The cycling interaction of myosin heads with actin causes sliding followed by muscle contraction. A dissociated myosin head hydrolyzes ATP, releasing ADP and phosphate.

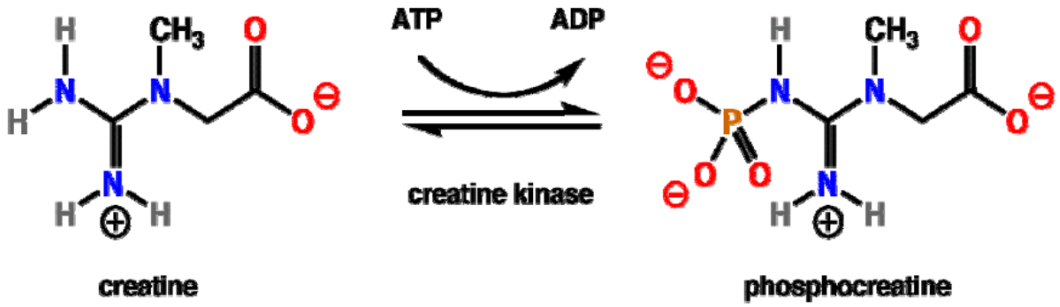


Figure: 2. Showing the catalytic reaction of Creatine kinase.

Myosin heads move over actin, inorganic phosphate is released from the active site of myosin, and the angle is changed to 45° from 90^0. This creates the power stroke and the actin filament can slide against the myosin filament. The myosin head dissociates from actin after liberation of ADP from the active site and binding of a new ATP molecule, and the cycle continues.

CREATINE KINASE MUSCLE BRAIN FRACTION:

Creatine phosphokinase (CPK) or phosphor creatine kinase is an enzyme expressed in many cell types. The EC 2.7.3.2 . CK catalyses the formation of phosphocreatine and Adenosine-5'-diphosphate (ADP) from creatine by utilizing ATP. This reaction is a reversible one.

Table:9 . The reference values for Creatine kinase and its isoenzymes. [27]

Age	CK	% MB	%BB
Cord blood	70-380 U/L	0.3-3.1%	0.3-10.5%
5-8 hour	214-1,175 U/L	1.7-7.9%	3.6-13.4%
24-33 hour	130-1,200 U/L	1.8-5.0%	2.3-8.6%
72-100 hour	87-725 U/L	1.4-5.4%	5.1-13.3%
Adult	5-130 U/L	0-2%	0%

At birth the CPK MB value will be 0.3 to 10.5 % of the CK. Value which ranges from 70 to 380 U/L. Hence the value above which the CPK-MB will be considered elevated is 3.1 multipled by the upper limit of normal i.e 380 U/L ,divided by 100 which gives 11.78 U/L.

Simillarly at 24 hrs the CPK-MB value will be 5% of 1200 U/L , which equals to 60 U/L. Therefore any value of CPK MB at 24 hours above 60 U/L is elevated..

At 72 hours of life, CPK-MB value above 39.15 U/L is elevated and considered above cut off value.

History of biochemical marker usage in myocardial injury

Time Period	Marker
Late 1950s	Aspartate-amino-Transferase [AST, SGOT]
1960s	Creatine Kinase [CK, CPK]
1970s	Creatine Kinase isoenzyme muscle brain fraction [CK-MB activity]
1970s	Lactate –dehydrogenase-isoenzymes [ratio of LDH1 to LDH2]
Late 1980s	Creatine Kinase-MB mass concentration
Mid 1990s	Troponin I, Troponin T

In 1985 Primhak et al observed in his study that “CK MB values peaked at 8 hours and fell by 72 hours of life”. The study involved asphyxiated (n=20)neonates and normal (n=43) neonates. Absolute and percentage CK MB Values were higher in babies with asphyxia.28

Sanchez-Nava et al showed in 1990 that among asphyxiated babies had raised AST, ALT and LDH [29].

In 1991 Omokhodion SI et al analysed creatine kinase and CK MB activities in first hundred hours of life in 23 perinatally asphtxiated newborns and 12 healthy controls. He observed that the asphyxiated infants had significantly elevated mean ck and absolute CKMB but not in fractional Ck MB values. Peak mean CK and CK mB values were 789.17±220 U/L, P less than 0.01 and 16.36± 3.0 U/L, P less than 0.001 respectively at the 6 to 8 postpartum period. On the other hand healthy controls showed a steady decline in the activities of these enzymes from birth[30].

Fonseca E et al in 1995 stated that "fetal distress in antenatal period is associated with release of CK BB, and particularly CK MB ; therefore, these parameters may be used as biochemical markers that may indicate either brain or myocardial damage".[31]

Lackmann et al concluded in 1996 that "newborn infants with asphyxia have significantly higher values of AST, LDH and hydroxybutyrate compared to neonates with only RDS, and presence of RDS among asphyxiated neonates did not alter the enzyme levels."[32]

In 1999 Barberi et al reported that “CK, CK MB ,CK MB/CK ratio and LDH were all increased in an asphyxiated group, while in a group with respiratory distress only CK MB and the CKMB/CK ratio were abnormal”.[33]

Primhak et al in 1985 and in 2000 Tapia-Rombo et al have shown in their studies what a high incidence of ischemic electrocardiographic changes, elevated blood cardiac enzyme levels and low cardiac output in neonates after intrapartum asphyxia.[34]

In 2000 Karunatilaka DH et al conducted a study in sri lanka to identify those infant s at risk of developing HIE or a major handicap following perinatal asphyxia by determining CK alone or in combination with LDH.analysis showed both CK and LDH were raised but only raised CK levels correlated with long term outcome.[35]

In 2005, Boo NY et al showed that at birth , asphyxiated infants had significantly higher concentrations of cTnT and CK MB than controls.[36]

In 2008 Reddy et al concluded that raised LDH had 100% sensitivity, while CK MB had 100% specificity for asphyxia.[37] In 2008 Rajkumar PS et al found that the cardiac enzymes, cTnT and CK MB were significantly elevated in cases when compared with controls.the mean CK MB levels among cases and control s were 121±77.4 IU/L and 28.8±20.2 IU/L respectively. The specificity and sensitivity of CK MB were 56.5% and 75.7% respectively.[38]

Electrocardiograph:

Serial electrocardiograms and creatine kinase (CK) isoenzyme activities were studied prospectively in 20 asphyxiated term newborn infants and 43 normal neonates. By adapting a previously described grading system for ischaemic changes, a degree of electrocardiographic ischaemia was defined which occurred almost solely in asphyxiated infants. Infants with this degree of abnormality had significantly higher mean CK-MB and MM activities than other asphyxiated infants at 0, 8 and 28 hours. Histological changes of peripartum myocardial necrosis were seen in 4 of the 5 infants on whom an autopsy was performed, and either electrocardiogram or CK-MB was abnormal in all four. It is concluded that myocardial injury in the newborn period is often associated with CK-MB release, but in view of the lack of cardiac-specificity of CK-MB in newborn infants, caution is urged in the interpretation of elevated isoenzyme activity in the neonate.

Perfusion index:

Newer pulsoximeters are able to measure and display the perfusion index. These indexes are shown to be a valuable tool to show serious illness in newborn. The perfusion index changes according to the sympathetic discharge, pain stimulus and in specific to decreased peripheral perfusion. Measurement of SpO2 by pulsoximeter is based on the absorption of two different lights. For this purpose red lights represented as R and infrared lights represented as IR are produced using LED technology in a pulsoximeter. Emitter provides these lights and is absorbed by blood,tissues and skin inbetween. The remaining is absorbed by the photodector on the opposite side. Blood flow varies with systole and diastole and hence the blood volume in the tissues. The ratio of light that is absorbed by the photodetector during these two phases of blood flow is converted to the oxygen saturation measurements.

PI is measured by dividing the variable or pulsatile IR signal (AC) by the nonpulsatile or constant IR signal (DC) and multiplied by 100. The IR signal has the advantage of being minimally affected by the oxygen saturation and hence is used in calculation of perfusion index.

$$PI = \{AC/DC\} \times 100$$

Echocardiography:

The role of two-dimensional Doppler - echocardiography is emphasized in establishing the diagnosis. Tricuspid insufficiency due to perinatal asphyxia can be detected easier by ultrasound than by any other cardiac examination. Cardiac failure as a result of hypoxic myocardial ischemia is usually reversible and responds well to anticongestive treatment and administration of oxygen. On the other hand some cases can be fatal, histopathologic examination on the heart shows similarity to myocardial infarction.

ASSESMENT OF FETAL WELL BEING:

Fetal well being during labour and following delivery is being assessed in many ways. These include observing for the passage of meconium, electronic fetal heart rate monitoring via a cardiotocograph (CTG), Apgar score and the assessment of fetal acid base balance.

MECONIUM STAINING OF AMNIOTIC FLUID:

Heavy or thick meconium staining is considered a reliable marker of more prolonged or severe asphyxia episodes. Approximately 15 % of all labours there is a meconium staining. Meconium staining is present during labour in 11% of full term pregnancies where there is no evidence, other than the meconium, of asphyxia. However data suggests that only 0.4% of term infants with meconium staining during labour subsequently had cerebral palsy.Richey et al found no correlation between meconium stained amniotic fluid and lab parameters suggestive of Acute birth asphyxia (umbilical arterial pH , lactate and hypoxanthine).

This sign is poorly predictive of adverse outcome and in one study, more than half of infants who had early neonatal seizures (a possible indicator of intra partum asphyxia) showed no evidence of meconium staining. Additionally, if cerebral palsy is considered as the final state of a major asphyxia event in the perinatal period, then 99.6% of normal birth weight infants with meconium staining had no evidence of this condition.

ELECTRONIC FETAL MONITORING (EFM):

Continuous electronic fetal monitoring is widely accepted and used despite the fact it has not been shown to reduce perinatal mortality or asphyxia relative to auscultation by trained personnel but has increased the incidence of operative delivery.these monitors simultaneously record uterine activity and FHR for ongoing evaluation.

The following parameters of fetal monitoring are recorded and avaluated:

- Baseline heart rate - normal between 110 and 160 beats in a minute(bpm).This baseline value must be apparent continuously for a period of 2 minutes in any segment for a stretch of 10 minute . Fetal bradycardia is defined as a FHR < 110 bpm may result fromcongenital heart block with associated congenital heart malformations or maternal systemic lupus erythematosus. Baseline tachycardia defined as FHR >160 bpm and may result due to fetal dysrhythmia, hyperthyroidism, maternal fever or choioamnionitis.

- Beat-to-beat variability: in an awake term fetus the autonomic system constantly varies the fetal heart rate from beat to beat by approximately 5 to 25 beats /minute. Depression of the fetal central nervous system due to fetal immaturity, hypoxia, fetal sleep or specific

maternal medications such as narcotics, sedatives, beta blockers and magnesium sulphate injections may result in a reduced beat to beat variability.

- Accelerations of the FHR are reassuring , as they are during a non stress test(NST)

- Decelerations o the FHR may be benign or indicative of fetal compromise depending on the shape and timing in relation to uterine contractions.
    - Early decelerations
    - Late decelerations
    - Variable decelerations

A normal fetal heart rate trace in labour appears to be a good indicator that metabolic acidosis is not developing, but a severly abnormal trace with late decelerations in the fetal heart rate is associated with significant fetal acidosis in only about 50% of cases. A recent Cochrane review showed that there was a statistically significant reduction in neonatal seizures when EFM had been used, but no protective effect for 1 min apgar scores, rate of admission to neonatal units, perinatal death or cerebral palsy.

APGAR SCORE:

Apgar scores are a method of describing the condition of an infant at birth, originally described by Virginia Apgar. Heart rate, respiratory efforts ,tone, reflex activity and colour a score is established at 1 min and then at 5 min intervals as necessary (maximum score 10). (table 10).

Table: 10 Apgar Evaluation of Newborn Infants .

SIGN	0	1	2
Heart rate	Absent	Below 100	Over 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, extremities blue	Completely pink

The ICD -10 definition of birth asphyxia is dependent on the 1 minute-Apgar score. The 1 minute-Apgar score is the scoring done to the newborn exactly 1 minute after birth. 1 minute -Apgar score at of 0-3 defines severe birth asphyxia and an Apgar score of 4-7 indicates moderate asphyxia. There is much debate as to whether this definition is

of clinical use. More specifically with regard to prognosis, Apgar scores in individual cases do not appear to correlate well with outcome and hence are frequently interpreted incorrectly from a view of long term prognosis. Defining birth asphyxia by Apgar score is however useful in identifying a high risk group requiring further observation of their neurological conditions with an understanding that it overestimates eight folds the scale of the problem. A low Apgar score may be due to various other conditions, like maternal. Drug administration in labour and or due to immaturity of the baby.

Table:11 Factors Affecting the Apgar Score [39]

FALSE-POSITIVE (NO FETAL ACIDOSIS OR HYPOXIA; LOW APGAR)	FALSE-NEGATIVE (ACIDOSIS; NORMAL APGAR)
Immaturity	Maternal acidosis
Analgesics, narcotics, sedatives	High fetal catecholamine levels
Magnesium sulfate	Some full-term infants
Acute cerebral trauma	
Precipitous delivery	
Congenital myopathy	
Congenital neuropathy	
Spinal cord trauma	
Central nervous system anomaly	
Lung anomaly (diaphragmatic hernia)	
Airway obstruction (choanal atresia)	
Congenital pneumonia and sepsis	
Previous episodes of fetal asphyxia (recovered)	
Hemorrhage-hypovolemia	

The 1-minute Apgar score reflects the need for immediate resuscitstion the 5-minute score, and particularly the change in score between 1 and 5 minutes, is a useful index of the effectiveness of the resuscitative efforts taken. The 5-minute Apgar score also has prognostic significance for neonatal survival, because survival is related closely to the condition of the infant in the delivery room.

The Apgar scoring was created not for the purpose of predicting prognosis. Cerebral palsy children had normal Apgar score at birth and the incidence of cerebral palsy is low in infants with Apgar scores of -3 at 5 min (but higher than in infants with Apgar scores of 7-10). The Apgar score and umbilical artery blood pH both predict neonatal death. An Apgar score of 0-3 is uncommon but is a better predictor of neonatal death (in both preterm and term infants) than an umbilical artery pH of 7.0 or less ; the presence of both variables increases the relative risk of neonatal mortality in term and preterm infants.[39]

Table: [12] **Incidence of Neonatal Death in 132, 228 Singleton Infants Born at Term (37th wk of Gestation or Later) in Relation to Apgar Scores at 5 min of Age*** .

5-MIN APGAR SCORE	NO. OF LIVE BIRTHS	NO. NEONATAL DEATHS (RATE PER 1,000 BIRTHS)	RELATIVE RISK (95% CI)
0–3	86	21 (244)	1, 460 (835–2, 555)
4–6	561	5 (9)	53 (20–140)
7–10	131, 581	22 (0.2)	1

* Infants with 5-min Apgar scores of 7–10 served as the reference group. CI, confidence interval.

LONG TERM OUTCOME:

Among the infants who survive severe HIE, the sequelae include mental retardation, epilepsy, and cerebral palsy of varying degrees. The latter can be in the form of hemiplegia, paraplegia, or quadriplegia. Such infants need careful evaluation and support. They may need to be referred to specialized clinics capable of providing coordinated comprehensive follow-up care.ent strategy. The incidence of long-term complications depends on the severity of HIE. Up to 80% of infants who survive severe HIE later in life develop serious complications, 10-20% develop

moderately serious disabilities, and up to 10% are normal. Among the infants who survive moderately severe HIE, 30-50% may suffer from serious long-term complications, and 10- 20% with minor neurological morbidities. Babies who had from mild HIE tend to be free from any serious CNS complications.

Table:[13] Risk of death or cerebral palsy(CP) in infants >2500g with Apgar scores 0-3 at varying times from birth [data from Nelson & Ellenberg]

Age (min)	Death in first year(%)	CP >2500g (%)
1	3	0.7
5	8	0.7
10	18	5
15	48	9
20	59	57

4. MATERIALS AND METHODS

STUDY DESIGN:

Hospital based prospective study.

STUDY POPULATION:

All term neonates with features of encephalopathy admitted in sick neonatal ward of Government Tirunelveli medical college Hospital for a period of 8 months between January 2014 to august 2014 will be included.

METHODOLOGY:

All neonates included will be evaluated clinically and with chest x ray, biochemical analysis, microbiological analysis, neurosonogram for cause and outcome recorded as discharged or expired.

Term neonates who had suffered perinatal asphyxia and developed HIE will be enrolled for evauation of transient myocardial ischemia of birth asphyxia based on the inclusion and exclusion criteria given below.

Myocardial involvement will be assessed by clinical evaluation, CXR, ECG, Echocadiography (based on feasibility of transportation and vitals stability)and CPK MB assay.

INCLUSION CRITERIA:

Babies admitted in the hospital with evidence of asphyxia indicated by any three of the following:

(i) APGAR ≤3 at 5 minutes.

(ii) fetal heart rate < 60/min

(iii) Meconium stained amniotic fluid

(iv) need for positive pressure ventillation for >1 min

EXCLUSION CRITERIA:

- Preterm babies,
- Neonates with congenital malformation,
- Neonates mothers who would have recieved magnesium sulphate injection within 4 hours prior to delivery or recieved opioids (pharmacological depression) or any other form of sedation.

STUDY PROTOCOL:

After written consent from parents, all the neonates included in study had the following done:

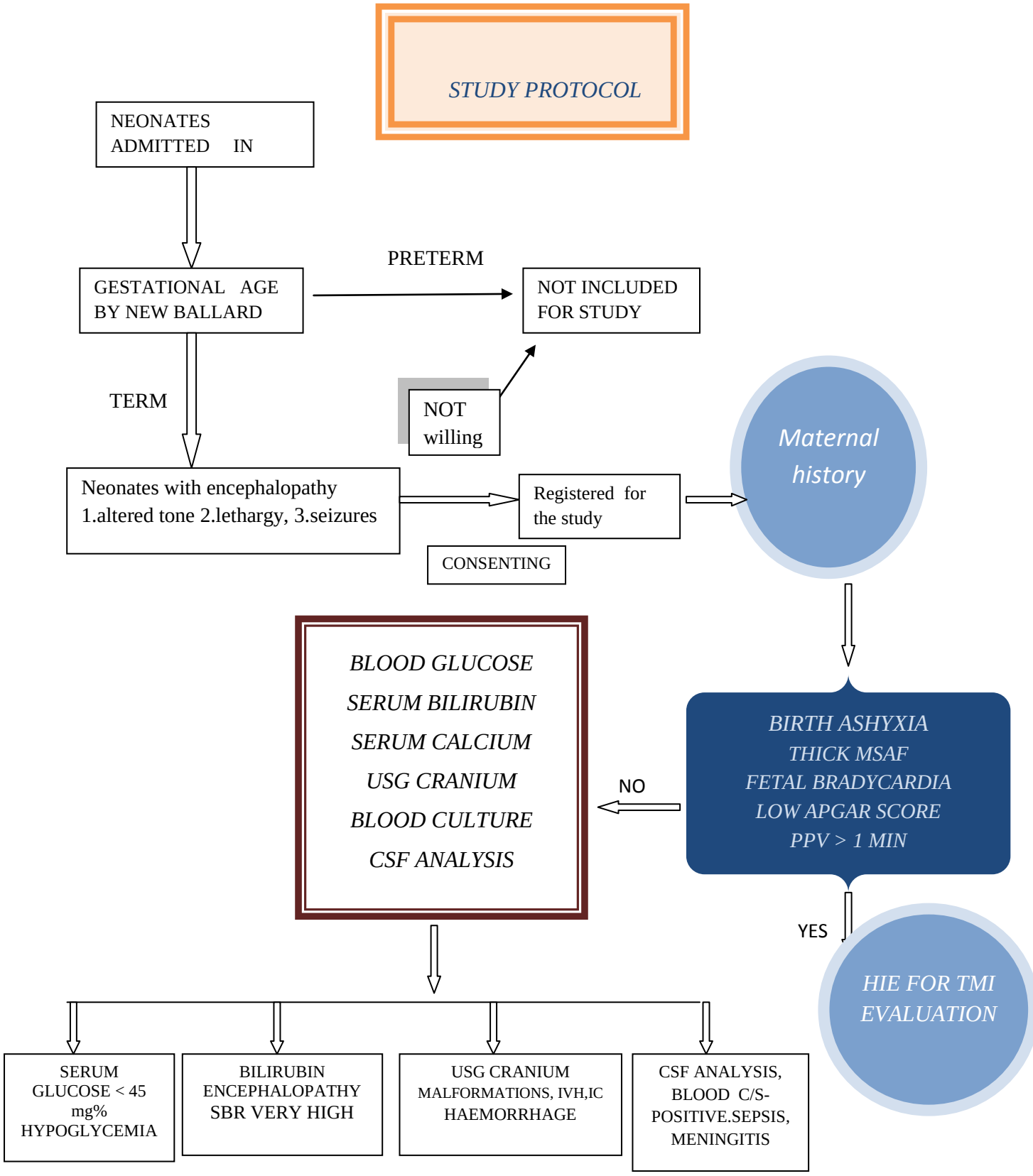
Detailed maternal history, details of meconium staining of amniotic fluid, birth events, APGAR score, Sex and weight of the baby recorded. Gestational age of baby assessed by New Ballard scoring system. Detailed clinical and neurological examination will be done. Non-invasive blood pressure, perfusion index using pulsoximetry will be measured.

Serum creatine phospho kinase MB assay will be done at birth, 24 hours and at 72 hours. Chest x ray will be taken to assses cardiomegaly, electrocardiography and where possible echocardiography based on transportability of newborn will be done.

Treatment as per existing institutional protocol will be given. Requirement of fluid boluses and duration inotrope support recorded. Outcomes of the disease recorded and analysed with details recorded.

STATISTICAL ANALYSIS:

Various causes, presentations of neonatal encephalopathy, methods used for diagnosis and outcome measured. CPK-MB assay along with ECG and clinical evaluation will be analysed to detect the relationship with HIE and death.


STUDY PROTOCOL
NEONATES ADMITTED IN
GESTATIONAL AGE BY NEW BALLARD
PRETERM
NOT INCLUDED FOR STUDY
TERM
NOT willing
Neonates with encephalopathy 1.altered tone 2.lethargy, 3.seizures
Registered for the study
CONSENTING
Maternal history
BLOOD GLUCOSE
SERUM BILIRUBIN
SERUM CALCIUM
USG CRANIUM
BLOOD CULTURE
CSF ANALYSIS
NO
BIRTH ASHYXIA
THICK MSAF
FETAL BRADYCARDIA
LOW APGAR SCORE
PPV > 1 MIN
YES
HIE FOR TMI EVALUATION
SERUM GLUCOSE < 45 mg% HYPOGLYCEMIA
BILIRUBIN ENCEPHALOPATHY SBR VERY HIGH
USG CRANIUM MALFORMATIONS, IVH,IC HAEMORRHAGE
CSF ANALYSIS, BLOOD C/S- POSITIVE.SEPSIS, MENINGITIS

TRANSIENT MYOCARDIAL ISCHEMIA - EVALUATION

Clinical shock with Inotrope requirement, New Systolic murmur, Perfusion index from pulsoximetry,

CXR-Cardiomegaly,

ECG-Ischemia,

ECHO-poor contractily, TR due to papillary muscle necrosis

CPK-MB ASSAY at birth, 24 Hrs & 72 Hrs

COLLABORATING DEPARTMENTS:

Departments of Biochemistry, Microbiology, Obstetrics, Radiology, Cardiology and Pathology; Tirunelveli Medical College, Tirunelveli.

LIMITATIONS OF THE STUDY:

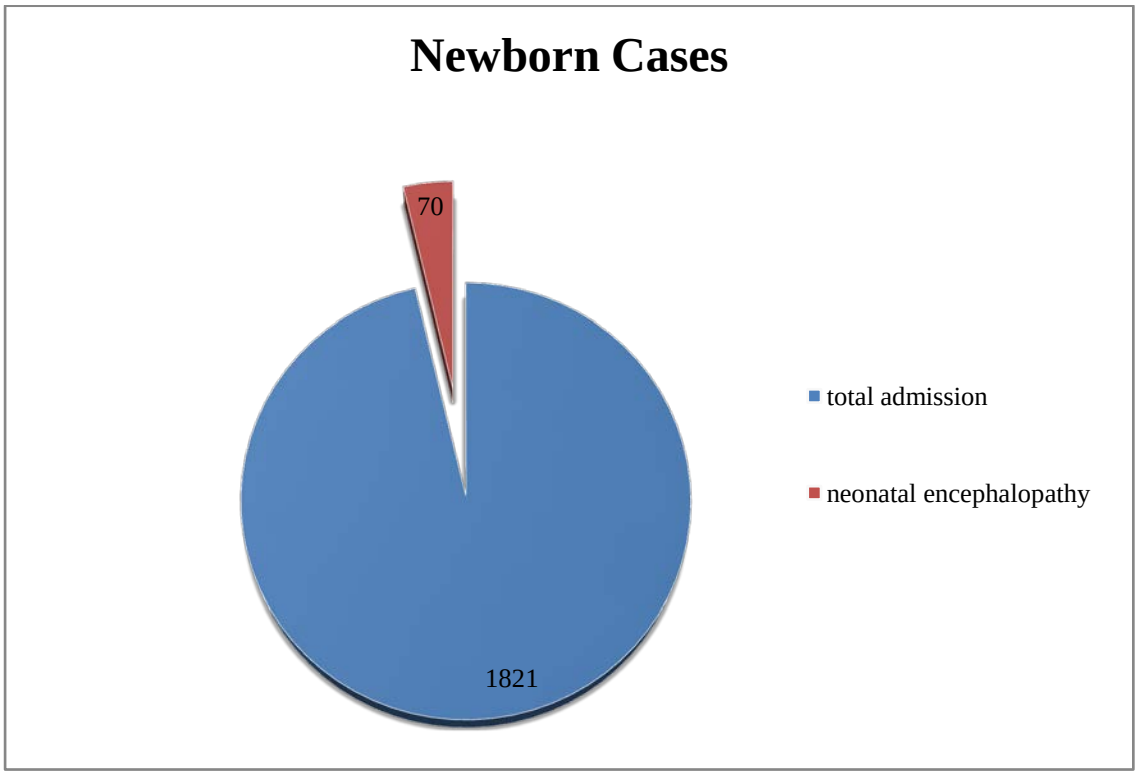
Echocardiography is considered as the gold standard test for assessing myocardial dysfunction but it was not done in all the HIE babies for evaluation of TMI.

STATISTICAL ANALYSIS :

Data was entered into an Excel Spreadsheet and analysed using SPSS Version 16. Using this software, frequencies, percentages, means, standard deviations, chi square test, paired t test, unpaired t test correlation were applied.. A 'p' value less than 0.05 is considered significant.

5. OBSERVATIONS AND RESULTS

PREVALENCE OF NEONATAL ENCEPHALOPATHY:



During the study period total admissions in sick neonatal ward was 1821 newborns. In this term babies with features of neonatal encephalopathy was 70 newborns.

The percentage of neonatal encephalopathy cases among the total admission is 3.84%.

SEX WISE DISTRIBUTION

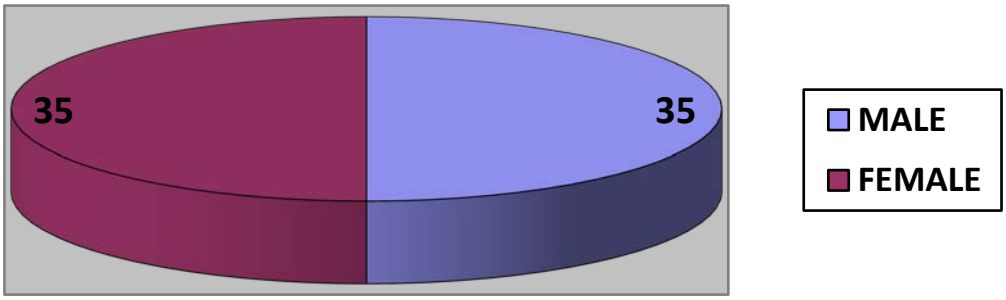


TABLE:14

S.NO	SEX	NEONATAL ENCEPHALOPATHY CASES (n=70)
1.	BOY BABY	35
2.	GIRL BABY	35

Among the 70 cases of neonatal encephalopathy 35 newborns were male and 35 were female. Both sexes having 50% contribution. Thus indicating no sexual

PLACE OF BIRTH IN NEONATAL ENCEPHALOPATHY:

INBORN AND OUTBORN :

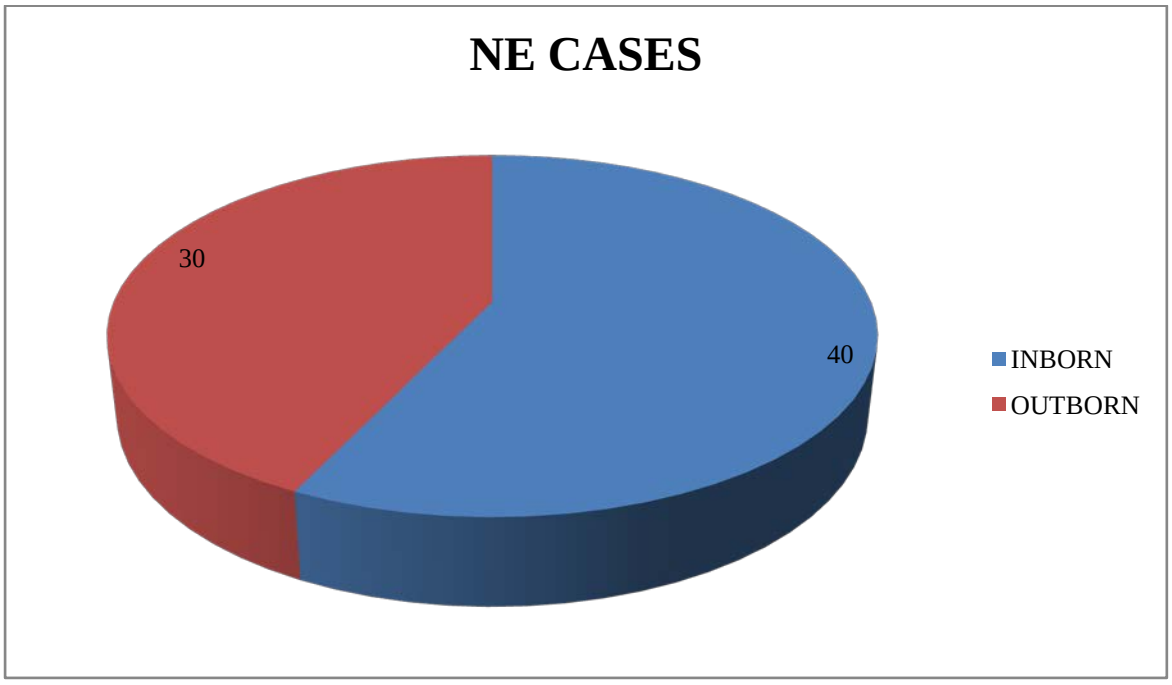


Figure 1 PLACE OF BIRTH

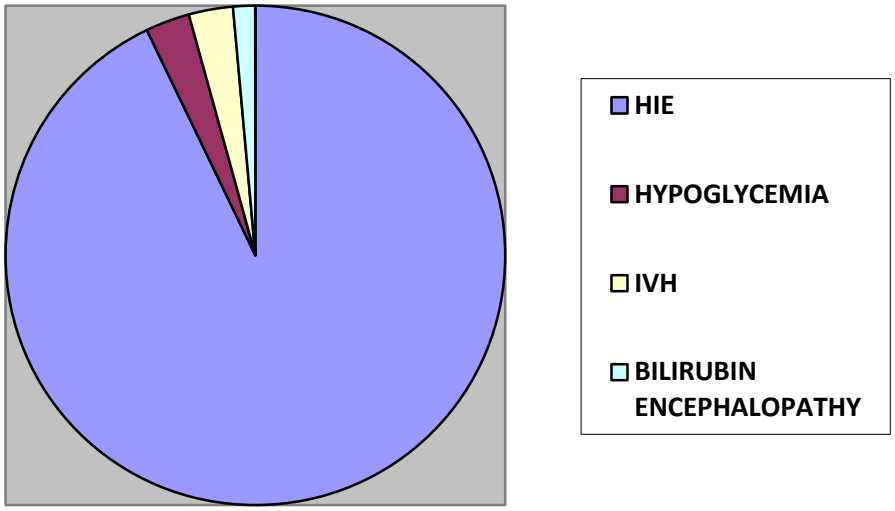
Among the 70 cases of neonatal encephalopathy, 40 babies were inborn (babies delivered in TVMCH) and 30 babies were out born (place of birth is not TVMCH, babies delivered either in PHC, Government hospitals, private nursing home, transit deliveries).

Table 15: PERCENTAGE OF INBORN AND OUTBORN CASES

S.NO	PLACE OF BIRTH	NE CASES (n=70)	FREQUENCY
1.	INBORN	40	57.14%
2.	OUTBORN	30	42.85%

Total number of term neonates with neonatal encephalopathy were 70. Number of babies with place of birth in TVMCH were 40, which account for 57.14%. The remaining 30 babies were outborn , having place of birth outside TVMCH. They account for 42.85% of the cases. The higher percentage of inborn newborn accounting for neonatal encephalopathy may be due to the presence of maternal risk factors and hence referral to tertiary institute before or during labour.

CAUSES OF NEONATAL ENCEPHALOPATHY:



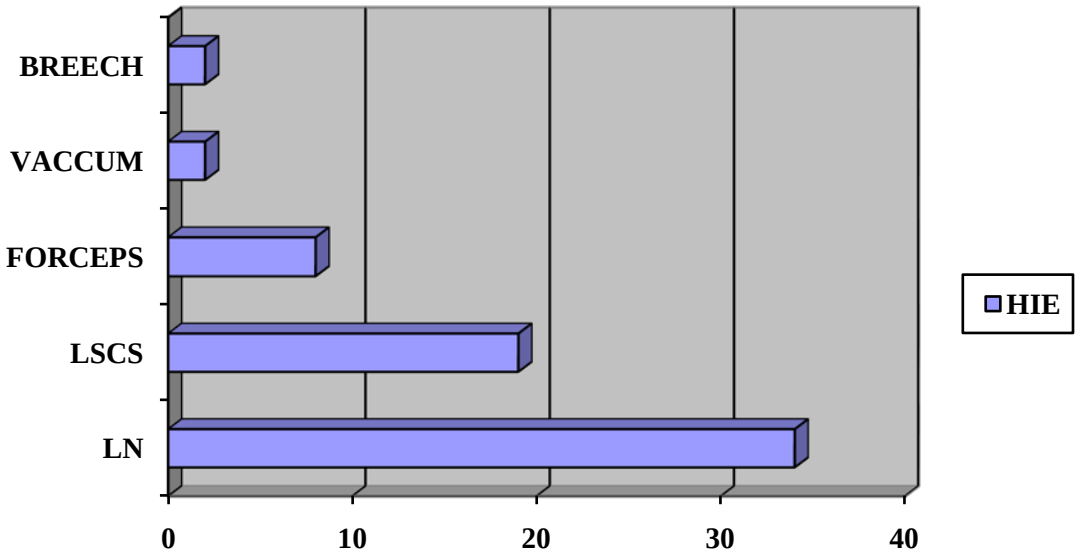
Among the term babies admitted in sick newborn ward, babies with features of neonatal encephalopathy were 70. Among the 70 newborn babies with neonatal encephalopathy, etiology were evaluated. 65 newborns had features of hypoxic ischemic encephalopathy, 2 newborns had hypoglycemia, 2 had intraventricular haemorrhage and 1 case was due to billirubin encephalopathy.

Table 16: ETIOLOGY OF NEONATAL ENCEPHALOPATHY

S.NO	CAUSES	NO. OFBABIES (n=70)	Frequency
1.	HIE	65	92.8%
2.	HYPOGLYCEMIA	2	2.8%
3.	INTRAVENTRICULAR HAEMORRHAGE	2	2.8%
4.	BILIRUBIN ENCEPHALOPATHY	1	1.4%

The HIE accounts for 92.8% of the neonatal encephalopathy cases admitted in our study period. The intraventricular hemorrhage and hypoglycemia each account for 2.8% (both having 2 cases each). 1 case of bilirubin encephalopathy accounted for the remaining 1.4%.

MODE OF DELIVERY IN HIE:



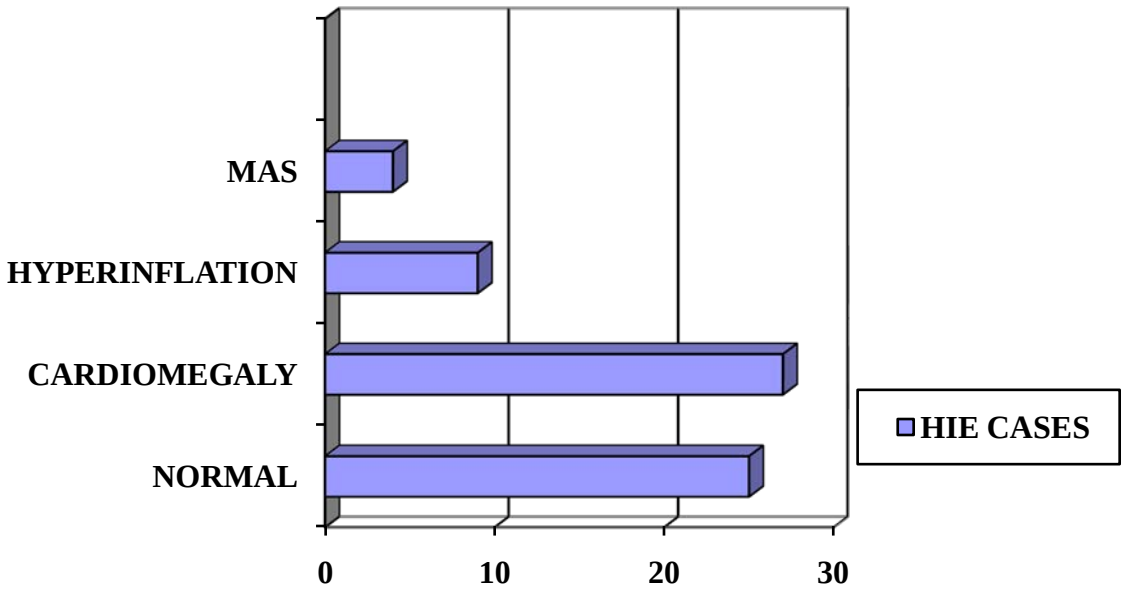
65 newborns had features of HIE. In this 65 babies 34 babies where born by labour natural with or without episiotomy. 19 babies delivered by lower segment cesarean section. 8 babies delivered by forceps assisted vaginal delivery. For 2 babies the mode of delivery was vaccum assisted vaginal delivery. Breech delivery was done in 2 other babies.

Table:17 MODE OF DELIVERY-PERCENTAGE

S.NO	MODE OF DELIVERY	No. OF HIE CASES (n=65)	FREQUENCY
1.	LABOUR NATURAL	34	52.30%
2.	LSCS	19	29.23%
3.	FORCEPS	8	12.3%
4.	VACCUM	2	3.07%
5.	BREECH	2	3.07%

As shown in the above tabulation, labour natural was the mode of delivery in 52.3% of newborns with HIE. 19 newborns delivered by Cesarian section and they account for 29.23%. 8 babies were delivered by forceps assisted vaginal delivery and they accounted for 12.3%. vaccum and breech deliveries were seen in 2 babies and they independently account for 3.07%.

CHEST- X RAY FINDING IN HIE CASES:



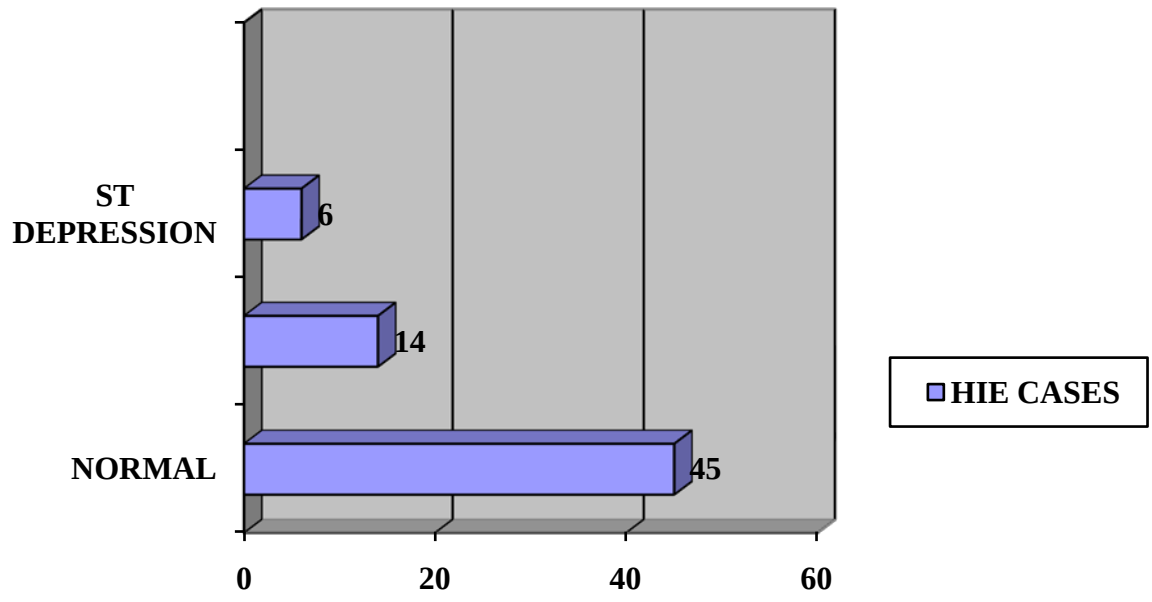
Chest x ray was normal in 25 babies with HIE. Cardiomegaly was the finding in 27 babies affected by HIE. Hyperinflated lungs was noticed in 9 mnewborns with HIE. Ches x ray of 4 newborns had features of meconium aspiration syndrome and air leak syndrome.

TABLE:18 CHEST X RAY FINDINGS IN HIE CASES

S.NO	CXR FINDING	HIE CASES (n=65)	PERCENTAGE
1	NORMAL	25	38.46%
2	CARDIOMEGALY	27	41.54%
3	HYPERINFLATED LUNGS	9	13.84%
4	MAS/AIR LEAK SYNDROME	4	6.15%

Cardiomegaly is seen in 41.54% of newborns with HIE suggestive of cardiac dysfunction. 25 newborns had normal heart and lungs in chest x ray accounting for 38.46%. hyperinflated lungs in 13.84% and MAS/ air leak syndrome in 6.15% accounts for the remaining.

ECG FINDINGS IN HIE:



45 out of total 65 newborns had normal ECG. They did not have any changes suggestive of ischemia. T wave inversion was noticed in ECG of 14 babies. ST segment depression was there in ECG of 6 newborns with HIE. These 2 ECG findings were suggestive of myocardial ischemia.

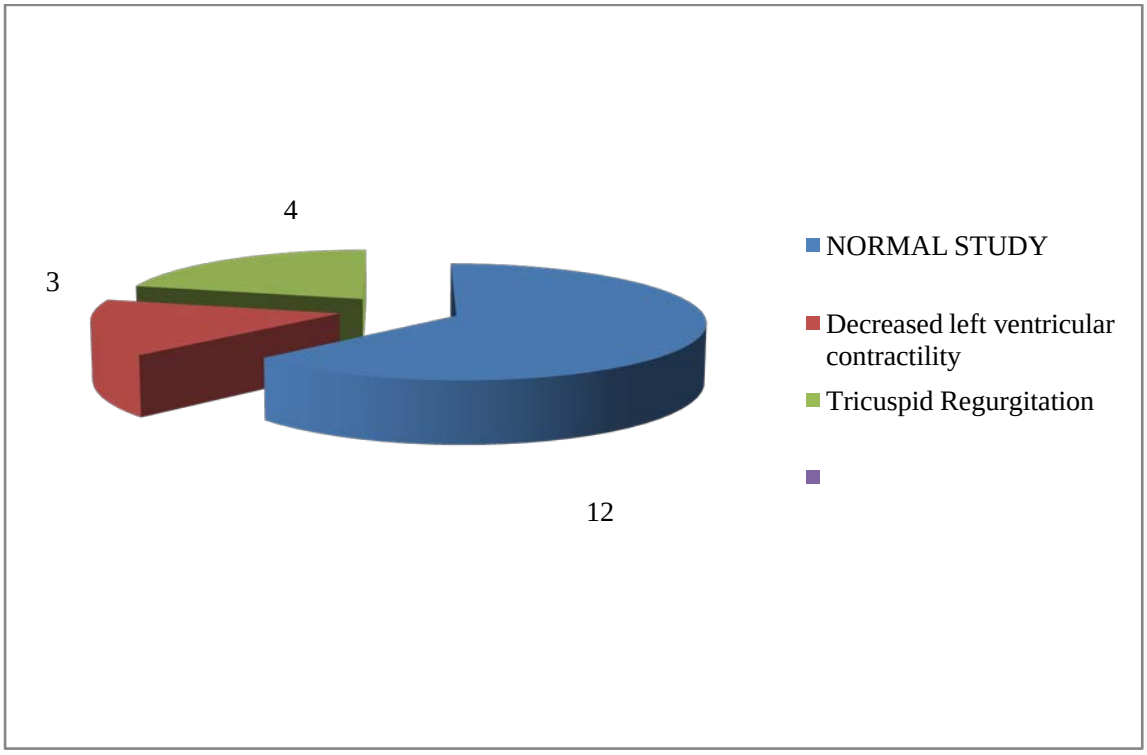
TABLE:19 ECG FINDINGS IN HIE CASES

S.NO	ECG FINDING	HIE CASES(n=65)	percentage
1.	NORMAL	45	69.23%
2.	T WAVE INVERSION	6	9.23%
3.	ST DEPRESSION	14	21.53%

Among the 65 cases with HIE evaluated ECG, 69.23% neonates had normal study. 6 neonates accounting for 9.23% of HIE affected neonates had T wave inversion in left precordial leads and 21.53 % (14 cases) had ST depression in midprecordial leads.

As both these changes indicate cardiac ischemia and they together account for 30.76%. Thus ECG positive finding is seen in nearly 31% of asphyxiated newborns.

ECHO FINDINGS IN HIE CASES:



Among the total 65 cases of HIE, echocardiography was taken in 18 babies.

12 babies were reported as normal heart without any structural or functional abnormality by the cardiologist. One baby had both tricuspid regurgitation and decreased left ventricular contractility. Three babies had TR alone and two other babies had decreased left ventricular contractility alone.

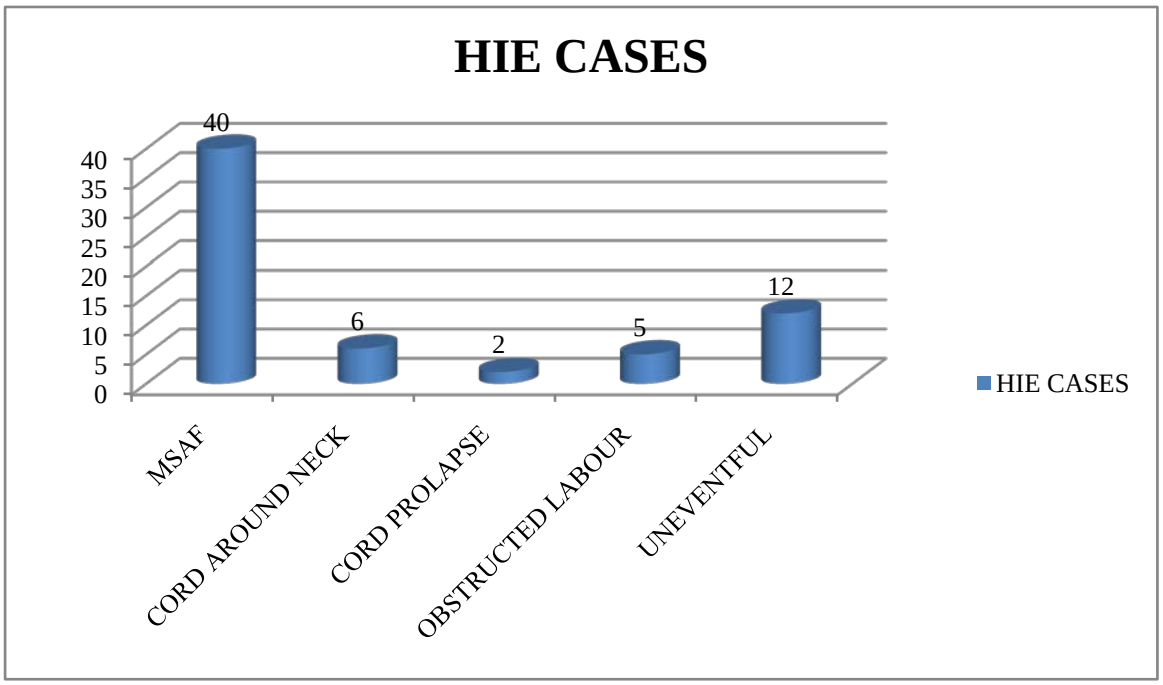
Thus the total cases with positive echocardiographic finding for ischemia are 6.

Table: 20 ECHO FINDINGS IN HIE CASES:

S.NO	ECHOCARDIOGRAPHIC FINDINGS	HIE CASES (n=18)	Percentage
1	Normal study	12	66.67%
2	decreased left ventricular contractility	3	16.66%
3	elevated ventricular end-diastolic pressures	0	0
4	Tricuspid regurgitation	4	22.22%
5	pulmonary hypertension	0	0

66.6 % of babies who underwent echocardiographic test had normal study. Tricuspid regurgitation is the commonest finding in echocardiogram seen in 22.22% (4 babies).

INTRAPARTUM EVENTS in HIE CASES:



Meconium staining of the amniotic fluid is the commonest intrapartum event. It is seen in 40 babies with HIE. Cord around neck noticed in 6 babies. Cord prolapse complicated labour in delivery of 2 babies. Obstructed labour occurred in delivery of 5 babies, whereas 12 babies had no adverse intrapartum events.

Table:21 INTRAPARTUM EVENTS in HIE CASES

S.NO	INTRAPARTUM EVENTS	HIE CASES (N=65)	PERCENTAGE
1.	MSAF	40	61.53%
2.	CORD AROUND NECK	6	9.23%
3.	CORD PROLAPSE	2	3.07%
4.	OBSTRUCTED LABOUR	5	7.69%
5.	UNEVENTFUL	12	18.46%

History of MSAF occurred in 61.53% of HIE babies. Cord prolapsed and cord around the neck together accounts for nearly 13% of HIE affected babies. 7.69% of babies had history of obstructed labour in there birth history. 18.46% of HIE babies had any of the intrapartum events.

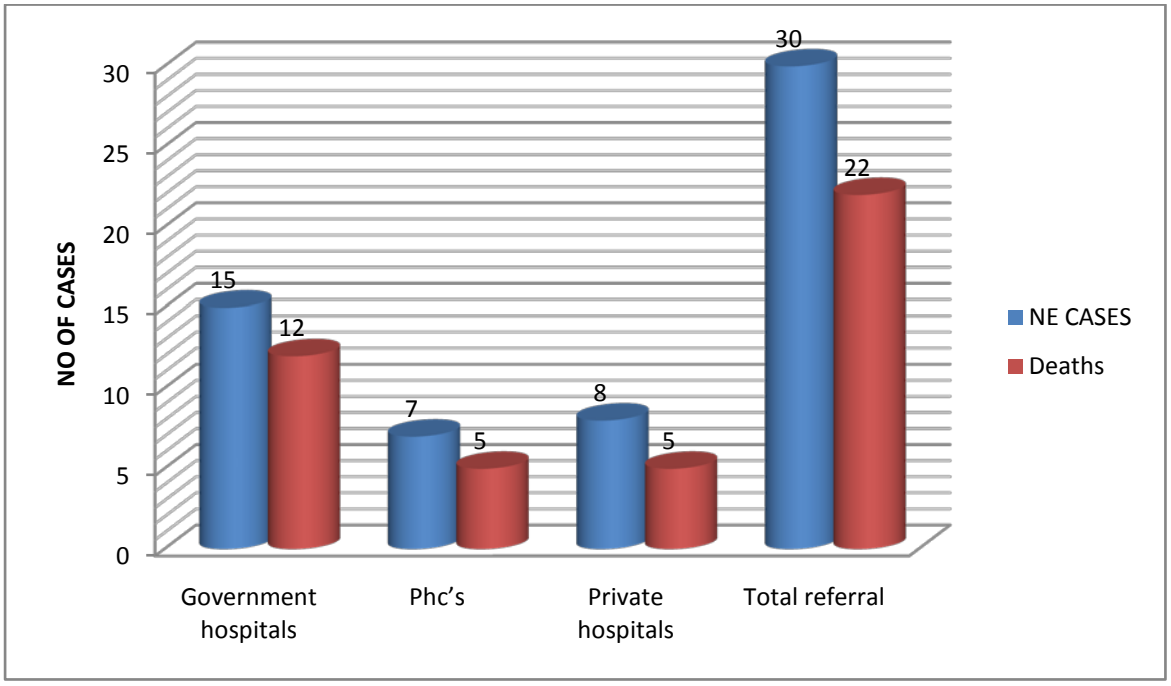
TABLE:22 OUTBORN BABIES – BIRTH PLACE

S.NO	PLACE OF BIRTH	HIE CASES	DEATH	PERCENTAGE contribution
1	GH	15	12	54.54%
2	PHC	7	5	22.72%
3	PRIVATE HOSPITALS	8	5	22.72%
TOTAL REFERRAL		30	22	100%

Among the outborn babies nearly 55% of the babies are from Government hospitals. PHC's account for 22.72% of cases. The remaining 22.7% of cases are from private nursing homes.

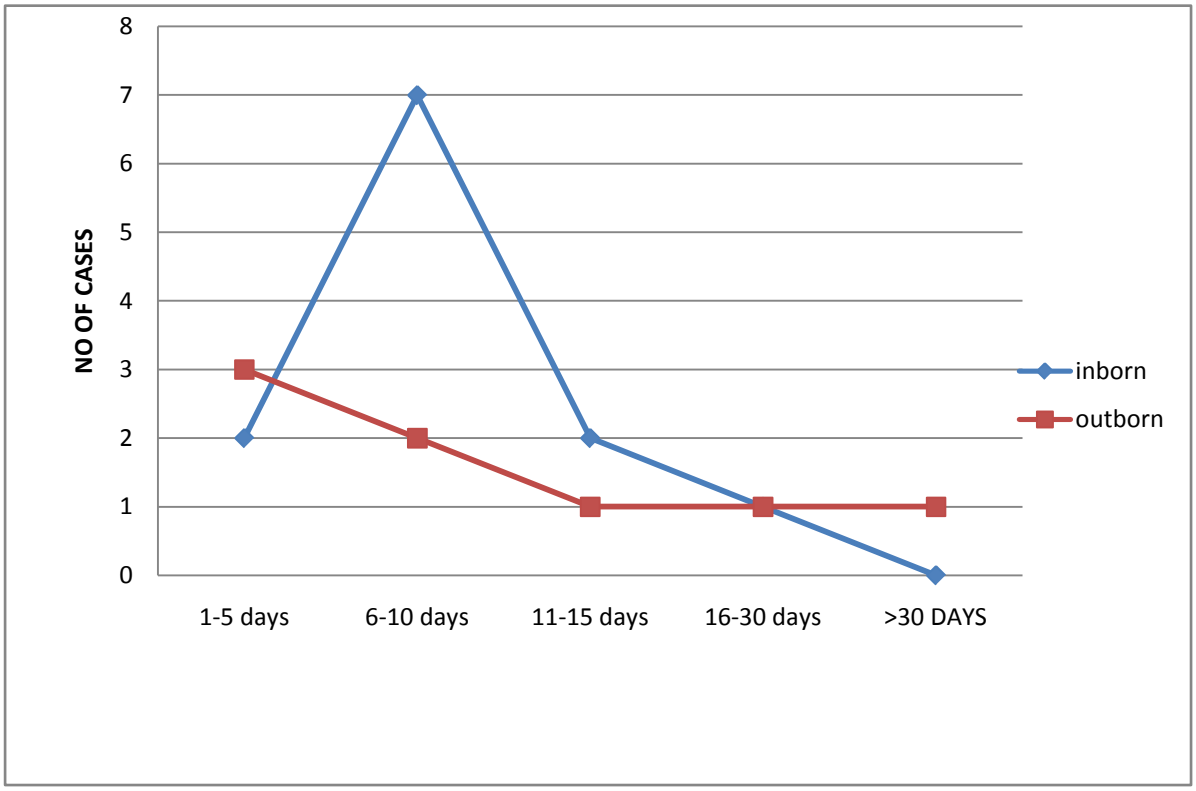
COMPARISON OF OUTCOME AMONG REFERRAL CASES

The chart shows number of babies referred from PHC, GH, private nursing homes along with corresponding number of deaths.



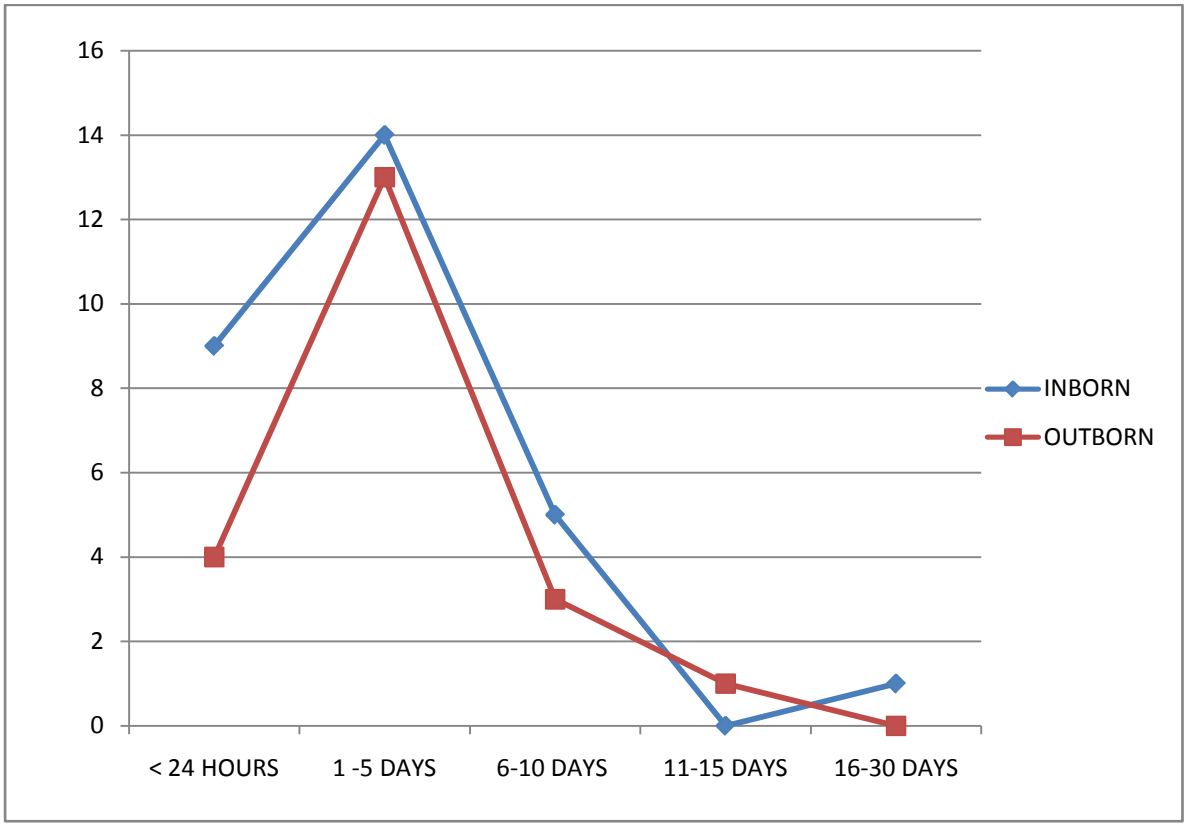
DURATION OF HOSPITALISATION AS INDICATOR OF MORBIDITY AND MORTALITY

IN DISCHARGED N.E CASES:



Maximum number of babies discharged after 6 to 10 days of hospitalization. Only 3 babies were discharged after 15 days of hospitalization . It accounts for 15% of the total discharged cases (3 out of 20 cases)

IN EXPIRED N.E CASES:



As shown in the graph, 4 outborn babies and 9 inborn babies expired within 24 hours of life. Maximum number of deaths (80%) occurred in the first 5 days in other words, 40 out of total 50 deaths happened in the first 5 days of hospitalization.

STATISTICAL ANALYSIS:

In Independent Samples Test, By applying Levene's Test for Equality of Variances and t-test for Equality of Means the relation between the following variables are assessed and interpretations are given.

Relation bw NE and gender

Interpretation

There is no significant difference in the occurrence of NE between male and female subjects and thus, there is no relationship between NE and the gender.

NE and primi

Interpretation

There is no significant difference in the occurrence of NE in the PRIMI and MULTI mothers and thus, there is no significant relationship between the NE and the PRIMI factor.

NE and labour natural vs LSCS vs assisted delivery(forceps,vaccum,breech)

Interpretation

a) There is no significant difference in the presence of NE and LSCS and instrumentation deliveries . Thus, there is no relationship between the NE and the LSCS or assisted delivery methods.

b) There is a significant relationship between the presence of NE in those who underwent natural labor and those who did not undergo natural labor. Those who underwent natural labor are more likely to have NE than those who did not undergo natural labor.

BIRTH weight and FD

Interpretation

There is no significant difference in the birth weight of the babies with and without fetal distress.

Birth weight and death

Interpretation

There is a significant difference in the birth weight of the babies those died and those did not die. The birth weight of the babies that died are less than those that did not die.

Relationship between the presence of NE and the death of the subject

Interpretation

Among the different NE cases, the cases with HIE3 are more likely to result in death than the causes that have other NE.

Relationship between PI and shock

Interpretation

According to the chi-square test, there is a significant association between the low PI and the occurrence of shock, but there is no significant association between the normal PI and the occurrence of shock. The cases with low PI are more likely to have shock than those without low PI. There is no significant difference in the occurrence of shock between the cases with and without normal PI.

Relationship between ECG output and the outcome

Interpretation

There is a significant difference in the outcome between the cases with and without negative ECG findings. The cases with negative ECG findings are more likely to be discharged than those without negative ECG findings.

Correlation between the APGAR score and the outcome

Interpretation

By using pearson correlation,an increase in the score at 10 mins would increase the chance of discharge by 28% and an increase in the score at 15 mins would increase the chance of discharged by 43.8% There is no significant correlation between the discharge of the subject to the score at 1 min and 5 minutes.

CORRELATION OF HIGH CPK-MB VALUE WITH OTHER TESTS:

A. Relationship between CPK MB HIGH score and shock

Interpretation

The cases with high CPK MB 24 hours are more likely to have shock than those without high CPK MB 24hours value. The other CPK values are not related to the shock occurrence.

B. Relationship between low PI and CPK MB HIGH value

Interpretation

There is a significant difference in the occurrence of high CPK value at 24 hours and 72 hours in those with and without low PI. The cases with low PI are more likely to have high CPK value at 24 hours and 72 hours. CPK value at birth has not significant difference in the cases with and without low PI.

C. **CPK-MB value and cardiomegaly**

Interpretation

There is no difference in the high CPK-MB value at birth for those with and without cardiomegaly. The cases with cardiomegaly is more likely to have high CPK-MB value at 24 hours and 72 hours than in the cases without cardiomegaly.

D. **CPK-MB value and the negative ECHO findings**

Interpretation

There is a significant difference in the presence of negative ECHO findings in those with and without high CPK-MB value. The cases with high CPK-MB value are less likely to have a negative ECHO finding.

Since the variable used is negative ECHO, the analysis is changed to show that high CPK-MB value are less likely to have a negative finding. So, on the converse, those with high CPK-MB value are more likely to get positive ECHO findings.

E. Relationship between CPK-MB value and ECG output Interpretation

There is a significant difference in the occurrence of positive ECG output between the cases with and without high CPK-MB values. The positive ECG findings are more likely to be found in the cases wit high CPK-MB value at birth, 24 hours and 72 hours; than those who do not fall under these categories.

RELATION BETWEEN CPK-MB AND LOW PI:

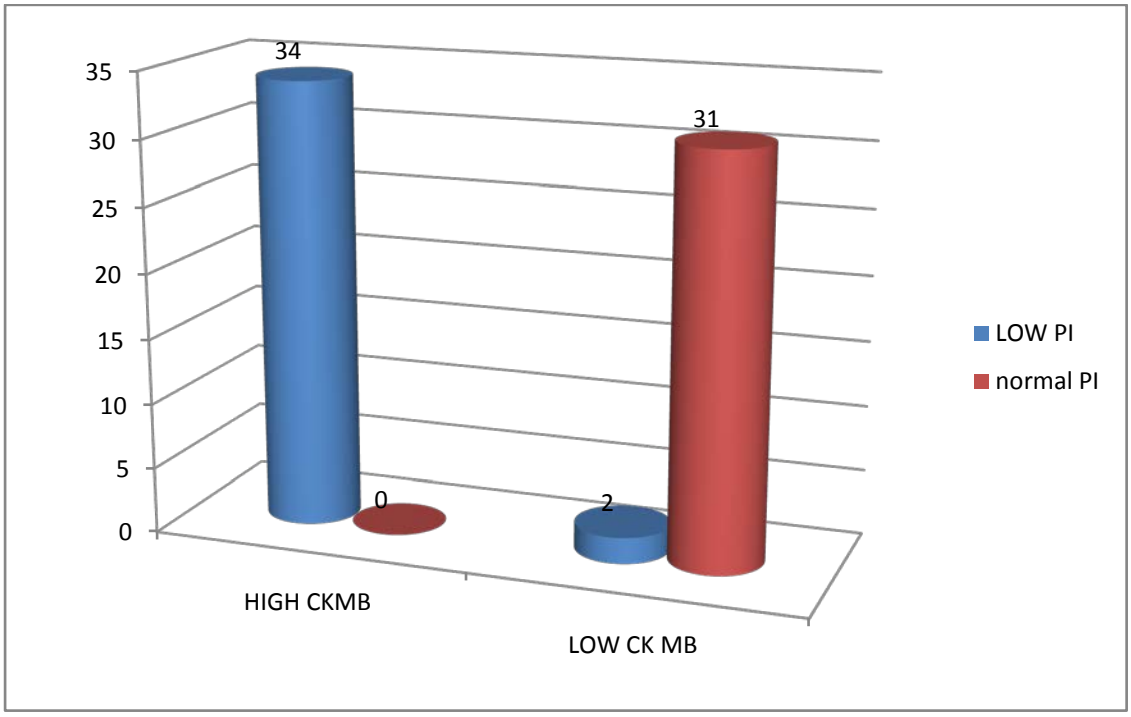
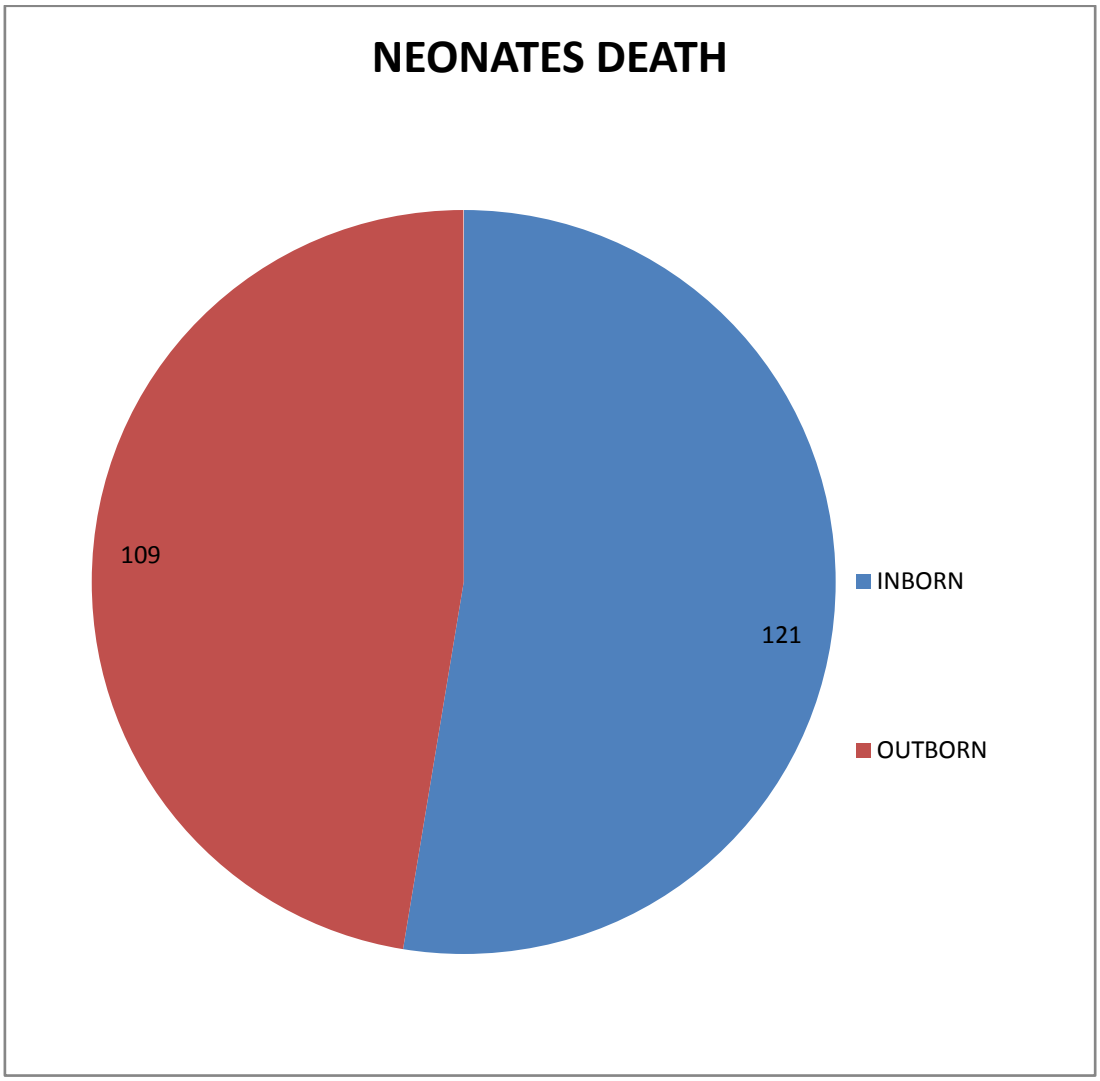


TABLE:23

	LOW PI	NORMAL PI
CPK-MB HIGH	34	0
	94.44%	0 %
CPK-MB LOW	2	31
	5.55 %	100%

As seen from the tabulation 94.44 % of babies with low PI had high CPK-MB values.

ALL CAUSES DEATH AMONG INBORN AND OUTBORN:

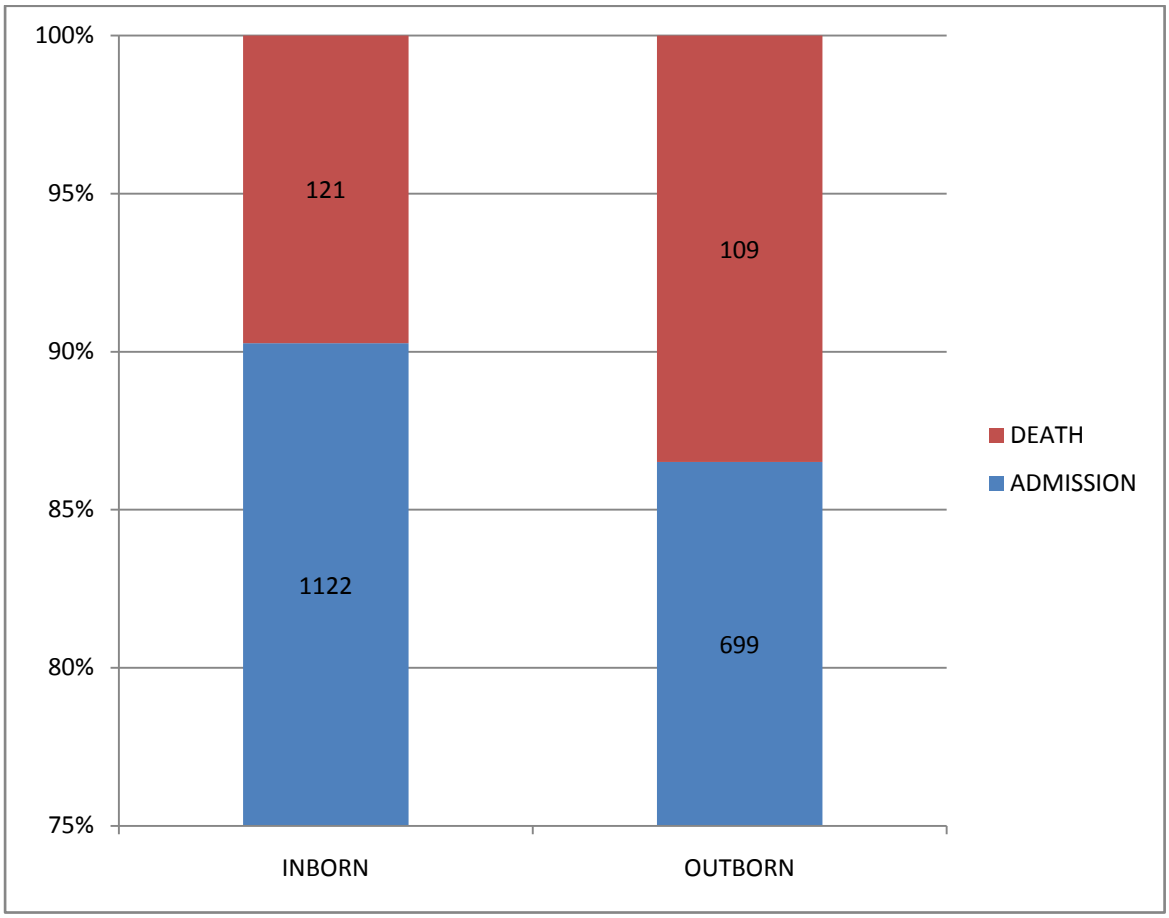


During the study period of January 2014 to august 2014, out of the total 1821 admissions in sick neonatal ward, 230 cases expired due to all cause.

TABLE: 24 ALL CAUSES DEATH AMONG INBORN AND OUTBORN:

S.NO	PLACE OF BIRTH	NEWBORN EXPIRED (n=230)	PERCENTAGE
1	INBORN	121	52.6%
2	OUTBORN	109	47.4%

COMPARISON OF ALL CAUSE DEATH IN INBORN AND OUTBORN



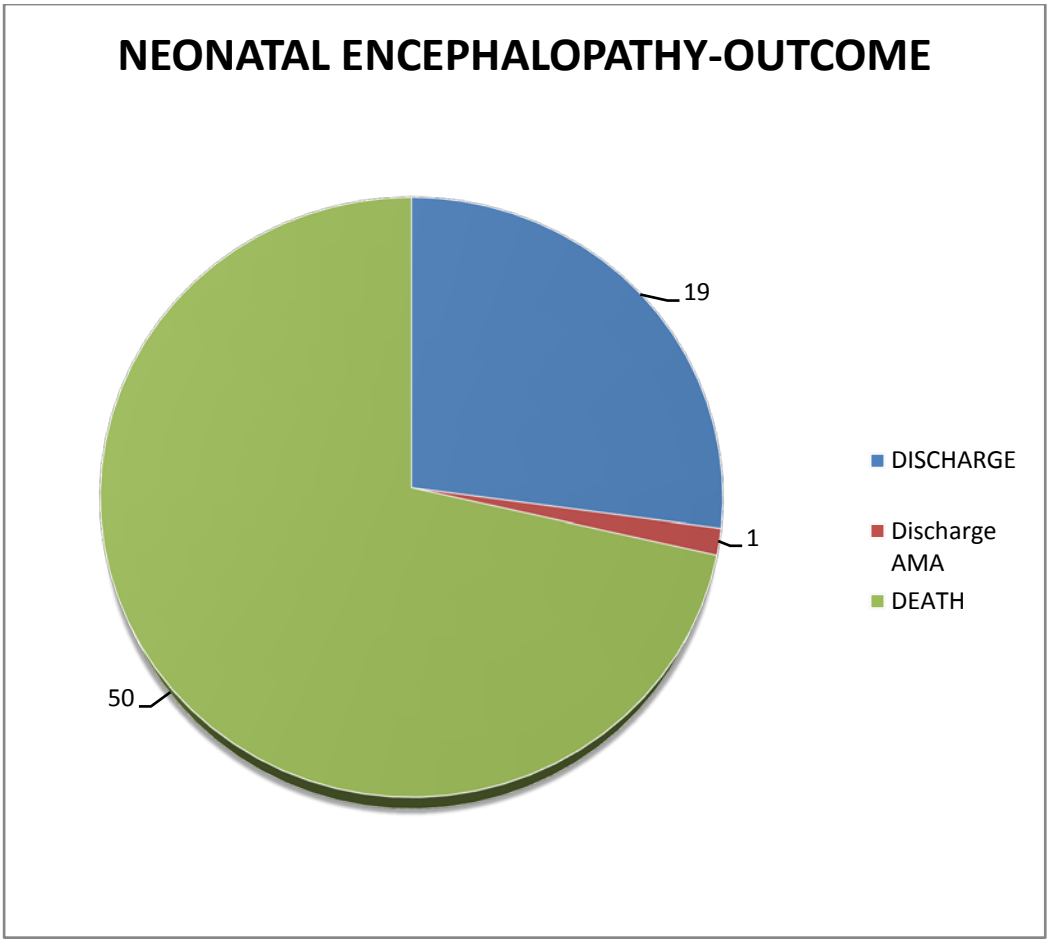
The above chart shows 121 cases expired out of total 1122 inborn babies admitted during the study period. In the outborn babies 109 babies died of all causes among the 699 admitted.

COMPARISON OF DEATH RATE AMONG INBORN AND OUTBORN:

TABLE:25

S.NO	PLACE OF BIRTH	ADMISSION (n=1821)	DEATH (n=230)	PERCENTAGE OF DEATH
1	INBORN	1122	121	10.78%
2	OUTBORN	699	109	15.59%

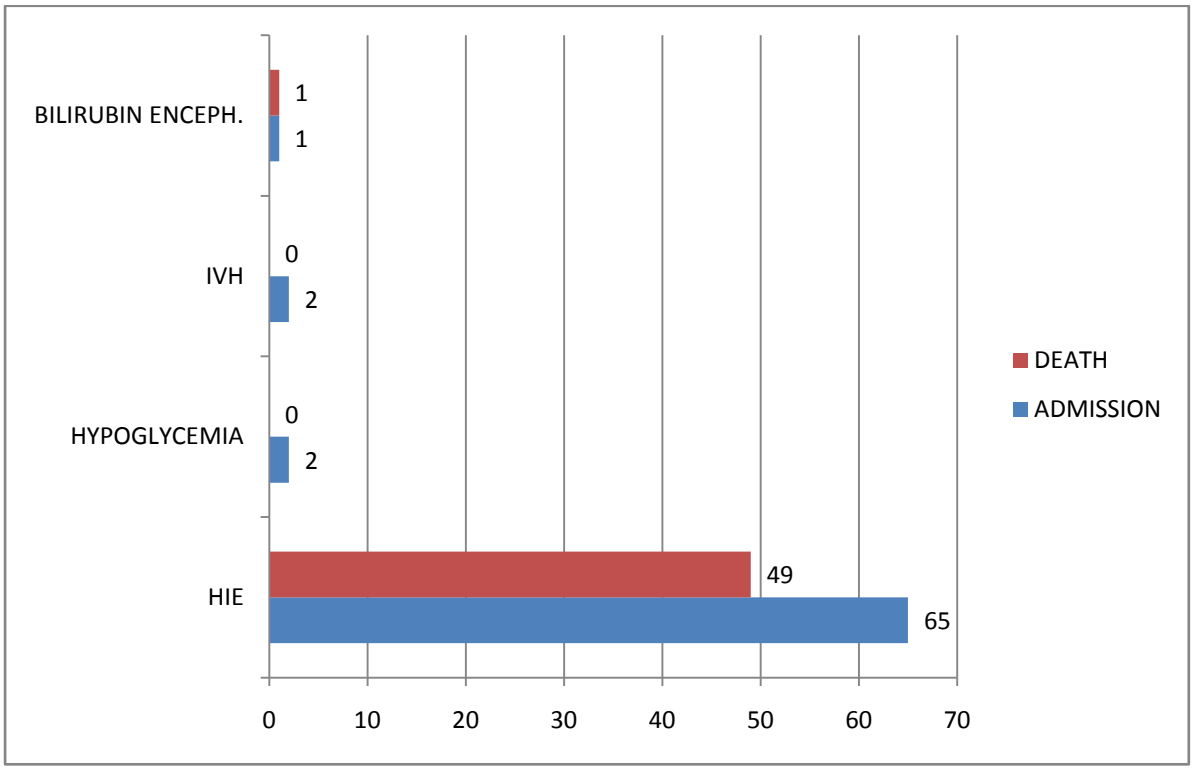
The above table shows that the death rate among inborn babies is 10.78% whereas the same figure in outborn babies is 15.59%.



Survival rate in NE:

Among the 70 cases admitted with neonatal encephalopathy, 50 babies expired and 20 discharged (including 1 baby discharged against medical advice). The survival rate among the neonatal encephalothy affected babies in our neonatal unit is 28.57 %.

ETIOLOGY WISE DEATH IN NEONATAL ENCEPHALOPATHY:



The above bar diagram shows the causes of neonatal encephalopathy and there mortality rate. In HIE 49 out of 65 babies admitted expired (75.4%). No death in encephalopathy cases due to hypoglycemia. Two other babies with intraventricular haemorrhage were also discharged alive. One case of bilirubin encephalopathy admitted on day 7 of life had clinical improvement but later developed sepsis and expired.

TABLE:26 ETIOLOGY AND DISEASE WISE MORTALITY

S.no	DIAGNOSIS	Cases(n=65)	Percent	Death(n=49)	%
1	Shock	30	46.15%	17	56.66%
2	Respiratory failure	29	44.61%	24	82.75%
3	Septicemia	8	12.30%	8	100%
4	AKI	1	1.53%	1	100%
5	NNEC	1	1.53%	1	100%

Shock and respiratory failure are the two major complications in HIE cases representing 46.15% and 44.6% respectively. While the respiratory failure caused death in 82.75% of the newborns having severe respiratory distress, the cardiac dysfunction resulted in 56% of the cases. Sepsis complicated with NNEC, AKI have increased the mortality rate.

6. DISCUSSION

Neonatal encephalopathy is a common condition in a neonatal intensive care unit. As discussed in literature, birth asphyxia (HIE) is the most common cause of neonatal encephalopathy. The 1-minute Apgar score predicts the survival chance of the neonate in the newborn intensive care unit. CPK MB values correlates to clinical development of shock and ECG changes of cardiac dysfunction. Here, critical analysis of the observations of our study is performed, comparing it with other Indian and foreign studies.

GENDER:

In the present study both genders have equal incidence of neonatal encephalopathy. In the study by Reddy S et al there is increased preponderance of male baby for birth asphyxia [36].There is neither a previous study available in this aspect nor a explainable mechanism available.

PARITY OF MOTHER:

There is no association between the birth asphyxia and parity of mother, which is comparable to Reddy S et al[36] and Khriesat WH et al[38].

MODE OF DELIVERY:

There is a significant relationship between the presence of NE in those who underwent natural labour and those who did not undergo natural labour. Those who underwent natural labour are more likely to have NE than those who did not undergo natural labour. This can be explained by the delay in the delivery and the prolongation of asphyxia associated with labour natural, LSCS can stop this asphyxia abruptly by immediate delivery.

But case control studies from Reddy S et al[36] and Khriesat WH et al[38] have shown more cases of LSCS in asphyxia cases than in the control group.

FETAL DISTRESS:

History of MSAF occurred in 61.53% of HIE babies. Cord prolapsed and cord around the neck together accounts for nearly 13% of HIE affected babies. 7.69% of babies had history of obstructed labour in there birth history. 18.46% of HIE babies had any of the intrapartum events. In 2010, an Indian study done in Rajiv Gandhi university Karnataka, had MSAF in 64% of cases.[40]

But only 8% of asphyxia babies had MSAF in Reddy S et al. The difference can be attributed to the inclusion criteria differences.

BIRTH WEIGHT AND DEATH:

The birth weight of the babies that died is less than those that did not die.

COMPLICATIONS IN ASPHYXIA:

In the present study, Shock and respiratory failure are the two major complications in HIE cases representing 46.15% and 44.6% respectively.

In the study by Reddy S et al[36] and Rajkumar PS[37] et al cardiogenic shock seen in 16% only, but Rajkumar PS et al study had CCF in 36.7% of cases and respiratory failure in 66.7% of cases.

Role of CPK MB :

Table: [27] Showing mean CK-MB levels (U/L) in cases and controls in different studies.

	Cases		Controls		P value
	Mean	SD	Mean	SD	
Reddy S et al [36] (CK-MB at 8 hours)	176.1	243	33	20.8	<0.001
Reddy S et al [36] (CK-MB at 24 hours)	49.6	36	20.8	7	0.009
Rajakumar PS et al [37] (CK-MB at 6 hours)	121	77.4	28.8	20.2	< 0.001
Omokhodion SI et al	16.36	3.0	-	-	<0.001
Warburton et al	328	-	-	-	-
Mandal Ravi et al	823.5	-	-	-	-

In the present study, only the CPK MB values at 24 hours have correlated with occurrence of shock. The cases with low PI are more likely to have high CPK value at 24 hours and 72 hours. The cases with cardiomegaly are more likely to have high CPK-MB value at 24 hours and 72 hours than in the cases without cardiomegaly. The cases with high CPK-MB value are less likely to have a negative ECHO finding. The positive ECG findings are more likely to be found in the cases wit high CPK-MB value at birth, 24 hours and 72 hours; than those who do not

fall under these categories. Thus there is definitely a role for CPK MB analysis in asphyxiated babies. Similar reports with good specificity and sensitivity for CPK-MB analysis are obtained in other studies as shown in tabulation.

MO RTALITY:

In our present study, out of 65 HIE babies admitted - 49 expired (75.4%). In the study by Rajkumar PS et al only 16% of babies expired. The high mortality in our study is due to difference in inclusion criteria.

Table: [28]. Showing diagnostic performance of CK-MB in different studies.

	Sensitivity	Specificity	PPV	NPV	AUROC
Reddy S et al [36] (CK-MB at 8 hours) (cut-off of 92.6 U/L)	36%	100%	100%	52%	0.82
Reddy S et al[36] (CK-MB at 24 hours) (cut-off of 60 U/L)	36%	100%	100%	52%	0.74
Rajakumar PS et al [37] (CK-MB at 6 hours)	56.5%	75.7%	-	-	-

ETIOLOGY AND DISEASE WISE MORTALITY

Shock and respiratory failure are the two major complications in HIE cases representing 46.15% and 44.6% respectively. While the respiratory failure caused death in 82.75% of the newborns having severe respiratory distress, the cardiac dysfunction resulted in 56% of the cases. Sepsis complicated with NNEC, AKI have increased the mortality rate.

7. CONCLUSION

Neonatal encephalopathy is a common condition in a neonatal intensive care unit. Hypoxic ischemic encephalopathy is the most common cause of neonatal enceophalopathy.

The etiological diagnosis of neonatal encephalopathy as HIE is easily made with proper and complete perinatal history.

Evaluation of asphyxiated babies with neurosonogram, CSF Analysis ,CT brain, MRI, EEG, Echocardiography, CPK-MB analysis are increasingly available in many tertiary institutes and teaching hospitals.

Mobilisation of the asphyxiated infant for CT, MRI, Echocardiography is the limiting factor.

Myocardial dysfunction in newborns following perinatal asphyxia is common. The incidence of transient myocardial ischemia is more frequent following severe grade of HIE.

Routine ECG monitoring of asphyxiated babies helps to detect myocardial dysfunction and hence the identification of shock.

Assay of cardiac enzyme markers CPK-MB helps to complement clinical evaluation for early identification of shock.

Serial measurements of CPK-MB may be done where feasible.

Measurement of CPK-MB at 24 hours is more useful than measurement at birth or at 72 hours of life.

The early detection and hence prompt initiation of treatment of condition will help in improving prognosis of these asphyxiated newborns.

Use of pulseoximeters which measure perfusion index is useful tool for recognition of shock.

Considering the transient nature of myocardial ischemia early initiation of inotrope support will improve the outcome.

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PROFORMA OF THE DISSERATION

Baby of :

Sex:

Date and time of birth:

Birth weight:

Assessment of gestational age:

METHOD	LMP	USG	NEW BALLARD SCORE
PERIOD OF GESTATION			

MATERNAL HISTORY:

Birth notes:

MECONIUM STAINING OF AMNIOTIC FLUID- YES /NO

APGAR SCORE	1 MIN-	5 MIN-	10 MIN-	15 MIN-

Examination of baby:

Head to Toe Examination:

Any obvious external congenital abnormalities:

Neurological examination:

Other systemic examination:

Course in NICU:

Fluid boluses: - yes/no

Inotrope support :– yes/no

Perfusion index :- low/ normal

Seizures :- yes/no

COomplications:

HIE STAGE:

INCLUSION CRITERIA		**YES**	**NO**
1.	5 minute APGAR score of ≤3.		
2.	fetal bradycardia / HR < 60/min		
3.	Meconium staining of amniotic fluid		
4.	positive pressure ventillation for >1 min		

EXCLUSION CRITERIA		YES	NO
1.	Gestational age < 37 weeks		
2.	major congenital malformation		
3.	Neonate's mother have recieved magnesium sulphate injection within 4 hours before parturition or received opioids /sedatives (pharmacological depression)		

INVESTIGATIONS:

CBC:

Chest - x ray:

ECG :

Neurosonogram:

Echocardiography:

Other investigations:

CPK-MB assay	BIRTH	24 HOURS	72 HOURS

OUTCOME: Discharge / Death

Duration of hospital stay:

KEY TO MASTER CHART

B/O	–	BABY OF
IP. NO.	–	INPATIENT NUMBER
BW	-	BIRTH WEIGHT IN KILOGRAMS
M	-	MALE BABY
F	-	FEMALE BABY
MH	–	MATERNAL HISTORY
P	-	PRIMI
G2	-	2 ND GRAVIDA
POB	-	PLACE OF BIRTH
IB	-	INBORN
OB	-	OUTBORN
MOD	-	MODE OF DELIVERY
LN	-	LABOUR NATURAL
LSCS	-	LOWER SEGMENT CESAREAN SECTION
FORC	-	FORCEPS ASSISTED
VAC	–	VACCUM
BRE	-	BREECH
FD	-	FETAL DISTRESS
F BRAD	-	FETAL BRADYCARDIA
OBST	-	OBSTRUCTED LABOUR

CP - CORD PROLAPSE

CAN - CORD AROUND NECK

MSAF - MECONIUM STAINED AMNIOTIC FLUID

APGAR - SCORE AT 1MIN,5 MIN, 10 MIN,15 MIN

RESUTN - RESUSCITATION DETAILS

ETS - ENDO TRACHEAL SUCTIONING

BMV - BAG AND MASK VENTILATION

INTU - INTUBATION

NE - NEONATAL ENCEPHALOPATHY

HIE - HYPOXIC ISCHEMIC ENCEPHALOPATHY

LEVENE'S STAGE

1- MILD HIE

2- MODERATE HIE

3- SEVERE HIE

IVH - I NTRAVENTICULAR HAEMORRAGHE

HG - HYPOGLYCEMIA

BIL. ENC. - BILIRUBIN ENCEPHALOPATHY

RD - RESPIRATORY DISTRESS

MAS - MECONIUM ASPIRATION SYNDROME

PT - PNEUMOTHORAX

SHO - SHOCK

RS - REFRACTORY SHOCK

BULG AF	-	BULGING ANTERIOR FONTANELLE
LETH	-	LETHARGY
SM	-	SYSTOLIC MURMUR
PI	-	PERFUSION INDEX
NRM	-	NORMAL
PF	-	POSITIVE FINDING
N	-	NEGATIVE
CPK-MB	–	CREATINE PHOSPHOKINASE MB FRACTION
		VALUES AT BIRTH, 24 HRS,72 HRS.
CXR	-	CHEST X RAY
CM	-	CARDIOMEGALY
ECHO	-	ECHO CARDIOGRAPH
DHS	-	DURATION OF HOSPITAL STAY
D	-	DAYS
HRS	-	HOURS
DIS	-	DISCHARGE
E	-	EXPIRED
COD	-	CAUSE OF DEATH
RF	-	RESPIRATORY FAILURE
RS	-	REFRACTORY SHOCK
SEPS	-	SEPSIS
EOS	-	EARLY ONSET SEPSIS

LOS	-	LATE ONSET SEPSIS
NEC	-	NECROTISING ENTERO COLITIS
AKI	-	ACUTE KIDNEY INJURY
DAMA	-	AGAINST MEDICAL ADVICE

MASTER CHART

																	CPK- MB				
S.No	NAME	IP.NO	SEX	BW	MH	PLACE	MOD	FD	APGAR	RESUSC	NE	CLINICAL	PI	CXR	ECG	ECHO	BIRTH	24 HRS	72 HRS	DURHS	OUTCOME cod
1	B/O selvi	541	F	2.8	P	IB	LSCS	MSAF	1,3,6	ETS	HIE 3	RF SHO	LOW	CM	P	ND	14.4	66.8	NA	2 D	E/RS
2	**B/O Peratchiselvi**	75946	F	3.29	P	OB	LN	MSAF	1,2,6	INTU	HIE 3	RF	NRM	HIL	N	ND	3.6	42.2	21.4	4 D	E/RF
3	**B/O RAJALAKSHMI**	11407	F	2.2 KG	G2	IB	LSCS	MSAF	3,6	ETSU	HG	LETH,HG	NRM	N	N	ND	NA	NA	NA	6 D	DISCH
4	**B/O NALATHAI**	12141	M	3.6	P	IB	FORCE	ABS	3,6	BMV	IVH	BULGAF	NRM	N	N	ND	NA	NA	NA	15 D	DISCH
5	**B/O NAGALAKSMI**	12814	F	2.98	P	IB	LSCS	MSAF	1,4,5,6	ETS	HIE 2	-	NRM	CM	N	ND	6.2	13.08	9.6	6 D	DISCH
6	**B/O SHANMUGATHAI, TWIN 2**	12921	F	1.9 KG	P	IB	LN	MSAF	3,6	ET	HG	LETH,HG	NRM	N	N	ND	NA	NA	NA	7 D	DISCH
7	**B/O KUPPAMMAL**	13606	F	2.48	G2	IB	FORCE	IUGR	1,3,5,7	ETS	HIE 2	-	LOW	N	N	ND	12	32.3	33	12 D	DISCH
8	**B/O SUNDHARI**	13645	F	2.8	P	OB	FOR	-	3,5,6	INT	IVH	BULGAF	NRM	N	N	ND	NA	NA	NA	15 D	DAMA
9	**B/O Basheethmaimoon**	1681	M	2.57 KG	G2	IB	LN	MSAF	1,2,4,6	INTU	HIE 3	SHO +	LOW	CM	P	N	15.7	72.2	46.4	8 D	E/RS
10	**B/O Sundhraselvi**	2406	F	2.89 KG		IB	LSCS	MSAF	1,2,3,6	INTU	HIE 3	RF	HIL	N	N	ND	8.3	43	NA	2 D	E/RF
11	**B/O Ponmani**	3968	F	3	G2	IB	LSCS	MSAF	0,3,5,6	INTU	HIE 3	RF	NRM	N	N	ND	22.1	NA	NA	4 H	E/RF
12	**B/O Pudiyalakshmi**	3930	F	1.92 KG	PRI	IB	LN	MSAF	1,3,5,6	INTU	HIE	RF	NRM	N	N	ND	4.06	NA	NA	5 H	E/RF

13	**B/O Tamilselvi**	4882	M	2.9	G3P 2L2	IB	BR	-	2,2,5,6	INT,C C	HIE 3	RF	NR M	HIL	N	ND	14.4	NA	NA	21 H	E/RF
14	**B/O Buvaneshwari**	4824	F	2.8 KG	P	IB	LN	MSAF	1,2,4,6	ETS	HIE 2	NEC	NR M	N	N	ND	8.2	32.4	NA	2 D	E/EOS
15	B/O Meritameri	4124	F	2.7 KG	P	IB	LN	MSAF	1,2,5,6	ETS	HIE 2	SHO	LO W	CM	P	P	14.2	66.2	46.8	8 D	DISC
16	B/o Loorthu	4167	M	3.1	G2	OB	LN	-	2,3,6	BMV	HIE 2	SHO	LO W	CM	N	N	18.2	32.8	24.1	4 D	DISC
17	B/O Saroja	5323	M	2.4	G3	OB	LN	-	1,2,6	BMV	HIE 2	SHO	LO W	CM	N	N	4.8	23.7	6.8	3 D	DISC
18	B/O Prabha	5610	M	3.5 KG	P	IB	LN	MSAF	2,3,4,6	INTU	HIE	RF	NR M	N	N	ND	8.4	34	25.4	12 H	E/RF
19	B/O RADHAMANI	6285	F	2.6	P	IB	LSCS	FAS	1,3,5,5	INTU	HIE3	RS	LO W	CM	NA	NA	14.2	NA	NA	1 H	E/RF/RS
20	B/O Rekha, S/O Ravi,	5914	M	3	P	OB	LN	F BRAD	2,3,5,6	ETS	HIE 3	RS	LO W	CM	P	P	16	73.2	46	5 D	E/RS
21	B/O REKHA,S/O Ganesh,	7054	M	3.6 KG	G2	OB	LN	MSAF	2,3,5,6	INTU	HIE 3	RF	NR M	N	N	ND	9.02	45.1	22.06	2 D	E/RF
22	B/O PARVATHY	5805	F	2.9 KG	P	IB	FOR	MSAF	1,3,6	INTU	HIE 3	SEPS	LO W	N	N	N	24.2	15.7	16.3	21 D	E/LOS
23	B/O Madathy,	6849	M	2.8 KG	P	IB	LSCS	CAN	0,2,3,6	INTU	HIE 3	SEPS	NR M	N	N	N	3.2	15.4	9.04	5 D	E/EOS/AK I
24	B/O Muppudathy	7697	M	2.2 KG	G2	IB	LN	MSAF	2,2,4,6	INTU	HIE 3	RF	NR M	CM	N	ND	6.4	22	NA	2 D	E/MAS
25	B/O Deivakani	7730	F	1.6 KG	G3	IB	LN	MSAF	2,3,5,6	INTU	HIE 2	RF	LO W	N	N	ND	8.2	21	NA	2 D	E/RF
26	B/O Subbulakshmi	8262	F	2.5 KG	P	OB	LN	MSAF	1,3,4,6	INTU	HIE 2	SHO	LO W	CM	P	ND	13.4	NA	NA	1 D	E/RS
27	B/O KALIYAMMAL	9072	F	2.5 KG	P	OB	LN	MSAF	1,3,5,6	BMV	HIE 2	SHO	LO W	N	N	ND	9.4	42.4	28.3	14 D	E/LOS/NE C

28	B/O IYYAMMAL	9632	M	3.2 KG	G2	OB	LSCS	MSAF	2,3,3,6	INTU	HIE 3	SHO,SM	LOW	CM	P	ND	40.9	NA	NA	1D 3 HR	E/RS
29	B/O DIVYA	16191	M	2.4 KG	G2	OB	LN	MSAF	1,3,5,6	ETS	HIE 3	RS,SM	LOW	NRM	P	ND	18.1	78.8	45.01	4D	E/RS
30	B/O MAHALAKSHMI	16035	F	2.2 KG	P	OB	LN	MSAF	1,2,3	ETS	HIE 3	RS,SM	LOW	CM	P	ND	12.2	66	NA	2D	E/RS
31	B/O ULAGAMMAL	8748	M	3 KG	P	IB	LSCS	MSAF	2,3,4,6	ETS	HIE 3	SHO	LOW	CM	N	NRM	88.9	22	20	6 D	DIS
32	B/O POONGODI	16550	M	2.74 KG	P	OB	LN	MSAF	2,3,6	INTU	HIE 3	RF	LOW	N	N	ND	5.9	12.8	-	3 D	E /RF
33	B/O KAVITHA	18384	F	2.4 KG	P	IB	LN	MSAF	1,3,6	INTU	HIE 3	RF	NRM	N	N	ND	4.04	16.7	_	2 D	E /RF
34	B/O LALITHA	20618	M	3 KG	P	IB	LN	-	2,3,6	INTU	HIE 3	RF,RS	LOW	P	P	ND	18.4	66.2	-	3 D	E /RF/RS
35	B/O LATHA	19679	M	3.4 KG	P	OB	FOR	MSAF	1,3,6	INTU	3	REF SHO	LOW	+	N	ND	14.6	88.4	-	2 D	E /RS
36	B/O SELVI	18273	F	2.6 KG	G2	OB	LSCS	-	1,2,6	INTU	3	RF	LOW	MAS	N	ND	3.06	14	-	2 D	E /RF
37	BO POOMARI	18276	M	2.3 KG	P	OB	LN	MSAF	1,3,6	ETS	3	LETH	LOW	N	N	ND	14.2	56.1	-	2 D	E RS
38	B/O SUNDHARI	13645	F	2.82 KG	P	OB	FORCEP	-	0,2,5,7	ETS	3	LETH	NRM	N	N	ND	2.8	13.8	20	7 D	E /SEPS
39	B/O RUBY	22863	M	2.78 KG	P	IB	LSCS	-	1,3,6	INTU	3	RS, sm	LOW	CM	+	ND	20.4	66	NA	3 D	E /RF
40	B/O UMARANI	23494	M	2.7 KG	G2L0	IB	LSCS	OBST	1,2,3,6	INTU	3	SHO	LOW	N	ND	ND	17.2	NA	NA	8 HRS	E /RS
41	B/O SELVI	27038	M	2.63 KG	G2L1	IB	LSCS	OLIG	2,3,4,5	INT,ADR	3	SHO,SM	LOW	CM, HIL	ND	ND	18.6	NA	NA	3 HRS	E /RS
42	B/O MUPPIDATHY	26729	F	2.63 KG	P	IB	FORCEP	MSAF	2,3,6	INTU	3	RF	NRM	MAS	N	ND	6	22	24.2	9 D	E /MAS

43	B/O SHEELASHANTHI	29030	M	2.5 KG	P	IB	LN	CAN	1,3,7	INTU	3	RF	NRM	N	N	ND	4.2	16.4	NA	1 D 6 HRS	E /RF
44	B/O PETCHIYAMMAI	26127	M	2.7 KG	P	OB	LN	MSAF	1,3,6	INTU	3	RF	NRM	N	N	NEG	4.8	NA	NA	3 HRS	E / RF
45	B/O GOPALAKIRUSHNAVAGAI	26624	M	3.28 KG	G3	OB	BREECH	-	0,3,5,6	INTU	3	SHOCK	LOW	CM	P	NEG	16.2	66	32	10 D	E / SEP
46	B/O MUTHULAKSHMI	28848	F	2 KG	G3	OB	LN	MSAF	2,3,6	ETS	2	-	NRM	MAS	N	NEG	4.6	13	25.2	8 D	E/MAS/PT
47	BO SUDHA	28841	M	2.8 KG	P	OB	VACCUM	CAN	2,3,6	ETS	2	SHO	LOW	CM	PR	P	21	78.2	46.8	5 D	E/RS
48	b/o essakyammal	29213	M	2.8	P	IB	FORC	-	1,3,5	INTU	3	-	NRM	HIL	N	ND	4.6	6.8	NA	3 D	E/RF
49	B/o valli	35217	M	2.7 kg	G2	IB	LSCS	OLIG, MSAF	2,3,6	ETS	2	-	NRM	N	N	ND	3.2	16.2	NA	2 D	E/EOS
50	B/o sridevi	35469	F	3.05 KG	P	IB	LN	F BRAD	2,3,4,6	INTU	3	REF SHOCK	LOW	CM	P	P	17.3	64.2	44	18 HRS	E/RS
51	B/O PREMA	37192	M	2.99 KG	P	OB	LN	MSAF	2,3,7	ETS	2	RD	NRM	N	N	ND	4.2	24.5	16.4	5 D	DISCH
52	B/O VINIMALA	37459	M	2.6 KG	P	OB	LN	CAN	1,3,5,7	ETS	2	SEPS	LOW	CM	N	P	18.2	68	43.2	36 D	DISC
53	B/O LOURTHMARY	39850	M	3 KG	G3	OB	LSCS	CAN	2,3,4,6	INTU	3	RF,RS	LOW	CM	P	ND	24.6	NA	NA	14 HRS	E /RS
54	B/ SANKARESHWARI	39983	F	2.6 KG	P	OB	VACCUM	MSAF	2,3,4,6	INTU	3	RF,RS	LOW	CM	P	ND	20.2	78.3	NA	2 D	E /RS
55	B/O PETCHYAMMAL	41751	F	2.2 KG	G2	IB	LN	MSAF	2,3,4,5	INTU	3	RF	NRM	N	N	ND	6.2	NA	NA	7 HRS	E/MAS/PT
56	B/O CHELLADURAICHI	40175	F	2.9 KG	P	IB	LSCS	F BRAD	0,1,3,6	INTU, ADR	3	SHO,RF	LOW	CM	P	ND	16.3	76.2	43.1	9 D	E/RS

57	B/O PUNITHA	41378	F	2.8 KG	P	OB	LN	CAN,FO	1,3,6	INTU	3	SHOCK ,RF	LOW	CM	P	N	13.4	79	56.3	26 D	DISCH
58	B/O SIVARANJANI	41473	F	3.2 KG	G3	OB	LN	CAN	2,3,6	BMV	2	SHO	LOW,S	CM	P	N	4.3	16.6	13	7 D	DISCH
59	B/O PITCHAMMAL	42615	M	2.6 KG	G2	IB	LSCS	CP	1,3,5,6	INTU	2	SHO	LOW	CM	N	N	22	78	46.8	20 D	DISC
60	B/O MARYTHANGAM	42928	F	3.4 KG	P	IB	LN	MSAF	1,3,5,6	INTU	3	RF	NRM	HIL	N	ND	16.2	78.4	NA	2 D	E/MAS/RF
61	B/O JEYA	44421	M	2.5 KG	P	IB	LN	MSAF	2,3,6	INTU	2	RD	NRM	HIL	N	ND	18.2	32	24	7 D	DISC
62	B/O MAGESHWARI	44417	M	2.3 KG	P	IB	LN	MSAF	2,3,4,6	INTU	2	RD	NRM	HIL	N	ND	3.4	14.8	NA	2 D	E /MAS /RF
63	B/O DEVI	46863	F	3.2 KG	G2	IB	LSCS	THICK MSAF	1,3,5,7	ETS	2	NO SHOCK	NRM	N	N	ND	5.2	7.2	7.04	3 D	DISC
64	B/O CHITHRA	45087	M	4.1 KG	P	IB	LSCS	MSAF	2,3,5,6	ETS	HIE 2	RD	NRM	HIL	N	ND	13.4	18.04	11.6	8 D	DISC
65	B/O SHAGAYAMADHA	45257	M	2.63 KG	G2	IB	FORC	MSAF	2,3,7	ETS	2	RD	NRM	N	N	ND	4.5	28	16.8	6 D	E / SEPS
66	B/O MADHAVI	45106	F	2.25 KG	G2 Rh	OB	LN	NIL	7,8	NIL	BIL.ENC	NNH/SEPS	NA	N	ND	ND	ND	ND	ND	12 D	E /BIL ENC/SEPS
67	B/O AKILA	45601	F	3.06 KG	P	OB	LN	MSAF	2,3,4,6	INTU	3	RF	NRM	MAS	N	ND	8.9	15.2	NA	2 D	E/MAS/RF
68	B/O KALIESWARI	46298	M	3.7 KG	G2	OB	FORCEPS	NIL	2,3,4,6	INTU	3	RF	NRM	HIL	N	ND	2.8	13.4	6.8	6 D	DISC
69	B/O ALAGUSUNTHARI	46306	F	3.35 KG	P	OB	LN	MSAF	2,3,5,6	ETS	3	REF SHO,SM	LOW	CM	P	ND	18	NA	NA	10 HRS	E/RS
70	B/O KALIAMMAL	46914	F	3.02 KG	P	IB	LSCS	MSAF	2,3,4,6	ETS	2	SHO	LOW	N	P	P	14.4	66.4	45.8	9 D	DIS